Boletín Médico del
Hospital Infantil de México

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CLINICAL CASE

Clinical, radiological, and molecular diagnosis of progressive fibrodysplasia ossificans

*Vianey Ordóñez-Labastida[1], Alan Cárdenas-Conejo[1], Juan C. Huicochea-Montiel[1], Guadalupe E. Paredez-Rivera[2], Alberto Hidalgo-Bravo[3], Lucero M.J. Monterde-Cruz[4], and María A. Aráujo-Solís[1]**

[1]Departamento de Genética, Unidad Médica de Alta Especialidad Hospital de Pediatría Dr. Silvestre Frenk Freund, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social (IMSS); [2]Servicio de Genética, Unidad Médica de Alta Especialidad Hospital de Oncología, Centro Médico Nacional Siglo XXI, IMSS; [3]Servicio de Genética y Genómica, Instituto Nacional de Rehabilitación; [4]Fundación Teletón México. Mexico City, Mexico

Abstract

Background: *Progressive fibrodysplasia ossificans is a rare genetic disease with heterozygous mutations (autosomal dominant inheritance) in the ACVR1 gene, which causes progressive heterotopic ossification in muscles, tendons, and ligaments, usually secondary to trauma. The ossification foci generate pain, joint ankyloses, and restricted movement. Congenital shortening and medial deviation first metatarsal of the foot is a distinctive feature. This report aimed to present an educational value case of a patient with clinical, imaging, and molecular diagnosis of progressive fibrodysplasia ossificans, recognized as a rare condition that severely affects the quality of life.* **Case report:** *We present the case of a 6-year-old female patient with lumps in the right scapular and dorsal region, progressive joint rigidity, and short first metatarsal medially deviated since birth. By imaging studies, we established the diagnosis of progressive fibrodysplasia ossificans. Sanger sequencing of ACVR1 reported c.617G>A (p.Arg206His).* **Conclusions:** *Confirmation of the diagnosis allowed genetic counseling, including a comprehensive explanation of the disease's natural history and measures to prevent its rapid progression.*

Key words: *Myositis ossificans. Diagnostic. Genetics. Genetic counseling.*

Diagnóstico clínico, radiológico y molecular de fibrodisplasia osificante progresiva

Resumen

Introducción: *La fibrodisplasia osificante progresiva es una enfermedad genética poco frecuente, causada por variantes patogénicas en estado heterocigoto (herencia autosómica dominante) en el gen ACVR1, que provoca osificación heterotópica progresiva en músculos, tendones y ligamentos, comúnmente secundaria a traumatismos. Los focos de osificación generan dolor, anquilosis articular y restricción del movimiento. Es característico el acortamiento congénito y la desviación medial del primer metatarsiano del pie. El objetivo de este reporte es presentar un caso de alto valor educativo de una paciente con diagnóstico clínico, imagenológico y molecular de fibrodisplasia osificante progresiva, reconocida como una condición infrecuente y que afecta de manera grave la calidad de vida.* **Caso clínico:** *Paciente de sexo femenino con tumoraciones induradas en la región dorsal y escapular, detectadas a los 6 años de vida. Cursaba además con rigidez articular*

Correspondence:
*María A. Aráujo-Solís
E-mail: tonyarasol@yahoo.com.mx

Date of reception: 02-05-2020
Date of acceptance: 21-07-2020
DOI: 10.24875/BMHIM.20000119

Available online: 03-05-2021
Bol Med Hosp Infant Mex. 2021;78(3):234-238
www.bmhim.com

progresiva y primer metatarsiano del pie acortado y con desviación en sentido medial desde el nacimiento. Por estudios de imagen se estableció el diagnóstico de fibrodisplasia osificante progresiva. Por secuenciación Sanger se reportó c.617G>A (p.Arg206His) en ACVR1. **Conclusiones:** *La confirmación del diagnóstico permitió ofrecer un asesoramiento genético integral, incluyendo una amplia explicación de la evolución natural del padecimiento y de las medidas preventivas para disminuir su rápida progresión.*

Palabras clave: *Miositis osificante. Diagnóstico. Genética. Asesoramiento genético.*

Introduction

The prevalence of fibrodysplasia ossificans progressiva (FOP) is 0.6 to 1.36 cases per million people worldwide, with no predisposition by ethnicity or sex[1]. It is caused by pathogenic variants in the heterozygous state (autosomal dominant inheritance) in the *ACVR1* gene (located in 2q24.1) that encodes the activin A receptor type I (ACVR1)[2]. The c.617G>A (p.Arg206His) mutation has been detected in 95% of the cases (classic form)[3].

The soft tissue (muscles, tendons, and ligaments) is continuously regenerated in healthy individuals on a daily basis and following trauma[4]. At the cellular level, this happens through various members of the transforming growth factor-beta family (TGF-β). TGF-β family members are classified as osteogenic such as bone morphogenic proteins (BMPs) and non-osteogenic such as activin A. In turn, activin A intervenes in the differentiation of interstitial myogenic and mesenchymal cells during muscle fiber regeneration[5].

In the classic FOP, a gain of function in the ACVR1 receptor produces the abnormal overactivation of the intracellular signaling pathway by non-osteogenic ligands, causing the transformation of soft tissue precursor cells into chondrocytes and osteoblasts, which are then responsible for heterotopic endochondral bone formation[4,6].

Heterotopic ossification mainly affects the axial, dorsal, and cranial skeleton. This process starts from the central part with progression towards the ventral, appendicular, and caudal regions[7,8]. Trauma, surgeries, and intramuscular injections damage the soft tissue and create inflammatory foci, which subsequently undergo heterotopic ossification, causing stiffness and limited movement of adjacent joints[9].

In patients with the classic form of FOP, shortening and medial deviation or monophalangism of the first metatarsal or both are present from birth[10]. Cervical vertebrae fusion (from C2 to C7), high and narrow vertebral bodies, short and wide femoral necks may also be present, as well as osteochondromas in the medial part of the tibia[11]. These patients frequently present thoracic insufficiency syndrome, which predisposes to frequent pneumonia episodes that are usually an important cause of mortality[8]. Also, they can show conductive hearing loss due to the middle ear's ossification, while sensorineural hearing loss is also reported due to the affection of the auditory nerve or the cochlea[7]. In the presence of clinical and radiographic suspicion of this disease, the diagnosis is confirmed by molecular studies in search of pathogenic variants in *ACVR1*[7,9].

This report aims to describe a patient with clinical, radiological, and molecular FOP diagnosis. Awareness of this pathology will allow timely identification of patients with this condition, thus, avoiding unnecessary interventions that worsen their already precarious quality of life.

Clinical case

We report the case of a 10-year-old female patient product of the second pregnancy of healthy non-consanguineous parents and with two apparently healthy siblings. At birth, the patient was hospitalized for 5 days for low birth weight (1700 g) and height (42 cm). Subsequently, the patient showed normal development during infancy and childhood, with no other relevant antecedents. At 6 years of age, two indurated tumors were identified: one of 3.5 cm in the right scapular region and another of 5.5 cm at the dorsal vertebrae level. The patient underwent an orthopedic evaluation, and the biopsy of these tumors concluded myofibromatosis. After performing the diagnostic procedure, the tumors increased in size. The patient also presented joint stiffness of the upper extremities, limitation for rotation and flexion of the neck, and severe scoliosis. The Rheumatology department ruled out inflammatory pathological conditions. The patient underwent reevaluation by the Medical Genetics department. Physical examination indicated that the patient's weight was found on the 10th percentile and height and head circumference on the 50th percentile. Also, the patient showed reduced neck mobility (rotation and flexion), shoulder, elbow, and wrist joints

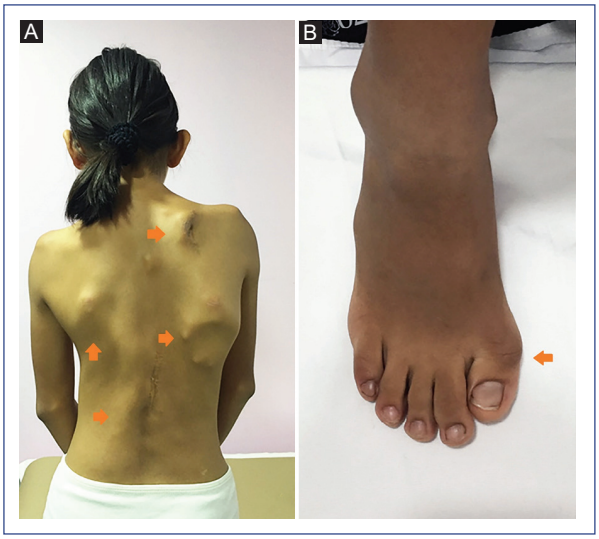

Figure 1. A. Back of the patient with ossification foci on scapulas, dorsal vertebrae (scars from previous surgical procedures), and body asymmetry by scoliosis. **B.** Shortening of the first toe with medial deviation.

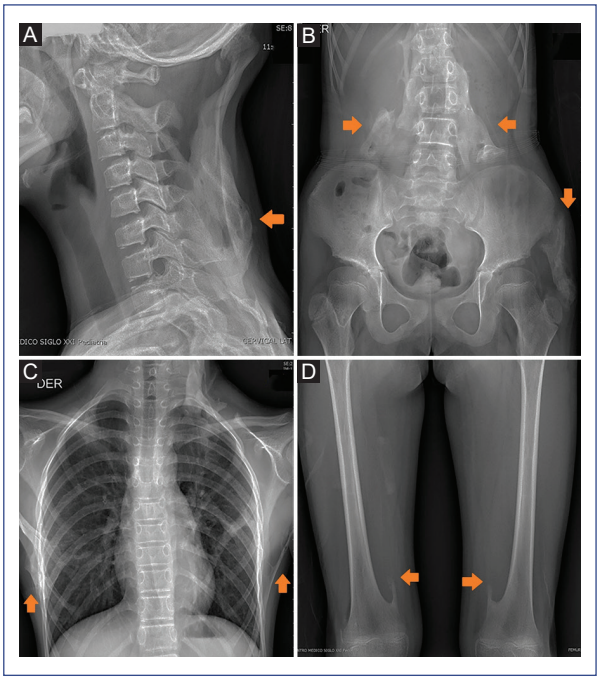

Figure 2. X-rays of the patient. **A.** Heterotopic ossification in the left cervical paravertebral region **B.** Heterotopic ossification in the lumbar paravertebral level bilaterally and the left coxofemoral joint. **C.** Heterotopic ossification in scapular and infraaxillary region **D.** Bone protrusions in femoral metaphyses due to heterotopic ossification of the iliotibial ligament.

stiffness, body asymmetry secondary to scoliosis, indurated tumors in the scapular and infrascapular areas (sites where biopsies had been performed), and a right infra-axillary tumor (Figure 1A). Short first toes with medial deviation were observed and present since birth according to the mother (Figure 1B). The anteroposterior feet X-ray showed bilateral fusion of the fourth and fifth metatarsals' proximal portion and shortening of the phalanges of the first toe with medial deviation. Dorsal, lumbar, and long bone X-rays showed soft tissue calcifications in several regions: the left cervical paravertebral region with an extension towards the left pectoral region (Figures 2A and 2C), the bilateral lumbar paravertebral level (Figure 2B), the left hip joint and femoral metaphyses bony projections (Figures 2B and 2D).

Computed tomography of the spine reported scoliosis, heterogeneous, poorly defined, multiple images with calcium depositions in the spine (bilaterally), trapezius, and back muscles (Figure 3).

The diagnosis of fibrodysplasia ossificans progressiva was established based on the radiological findings and physical examination. Subsequently, molecular studies were carried out at the Instituto Nacional de Rehabilitación (National Institute of Rehabilitation). Sanger sequencing of *ACVR1* reported the pathogenic variant in heterozygous state c.617G>A (p.Arg206His) in exon 6. Upon diagnosis confirmation, preventive measures were indicated, such as the use of protective cushions, administration of intramuscular injections only of vital importance, and not allowing surgical removal of the tumors.

The patient's last evaluation showed limitation of arm elevation above the 180° plane, difficulty in dressing and writing, and pain when remaining in a sitting or standing position for long periods. An audiological evaluation reported probable ossification of the middle ear ossicles. An MRI of the ear was indicated but has not been performed to date. The patient continues to be monitored by the Orthopedic and Rehabilitation services to treat scoliosis and for physical therapy and pain management with non-steroidal anti-inflammatory drugs, which, so far, have been sufficient to reduce the discomfort caused by tumors and joint stiffness.

Discussion

Based on clinical and radiological features and the molecular results of the *ACVR1* sequencing, the classic FOP form with the most frequently reported

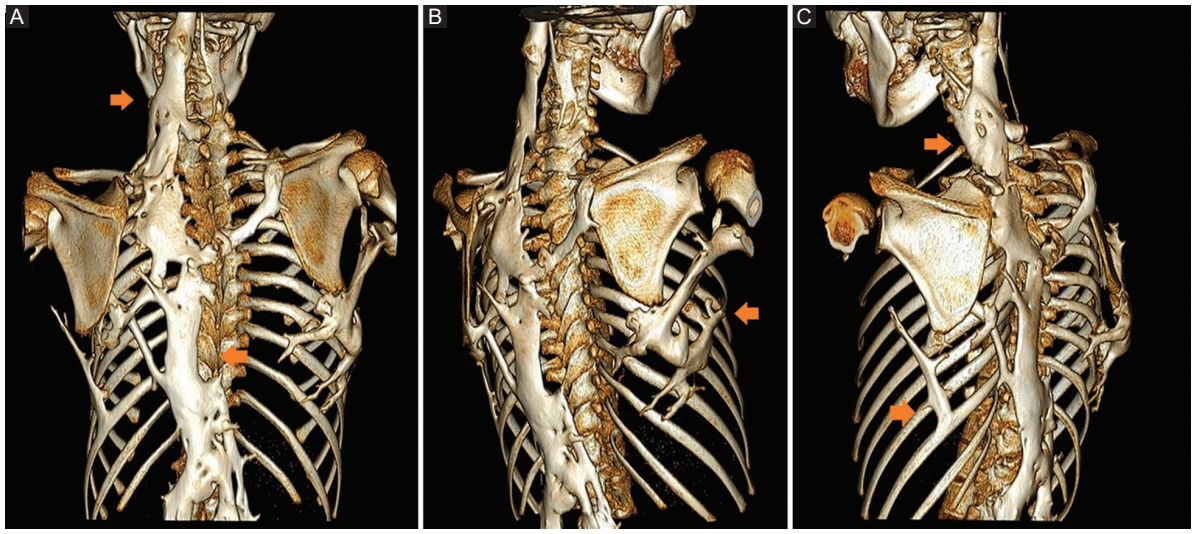

Figure 3. Tomography with a 3D reconstruction of the patient where heterotopic ossification is observed in posterior soft tissues, extending from the skull base to the lumbar region **(A)**, involving paravertebral and infrascapular muscles **(B)**. Fusion is observed along the tenth left posterior costal arch and dorsal kyphoscoliosis **(C)**.

pathogenic variant worldwide was diagnosed. The evolution in the present case is similar to previous reports in patients with the same variant, with heterotopic ossification foci appearing in the back, neck, and scapulas between one and 15 years of age, bilateral shortening with a medial deviation of the first toe since birth (virtually pathognomonic) and progression of the disease with the appearance of more ossification foci, and ankylosis limiting movement[12-14]. This mutation leads to the abnormal function of *ACVR1*, resulting in increased activation of the BMP pathway (osteogenic ligand) when exposed to the inflammatory stimulus secondary to trauma, giving rise to heterotopic ossification foci. FOP timely diagnosis allows avoiding unnecessary procedures that aggravate the clinical presentation. Due to late diagnosis, most patients have already undergone invasive studies that aggravate their condition. As this disease is highly disabling, it must be suspected in the presence of heterotopic ossification foci. Shortening of the first toe identification provides an excellent opportunity for clinical suspicion from the first years of life, allowing the differential diagnosis with entities that also present heterotopic ossifications, such as disorders of *GNAS* inactivation and Klippel Feil syndrome[15,16].

Once the FOP diagnosis has been established, the following preventive measures can improve the quality of life: restriction of physical activities to avoid falls or other traumas (without being strict, since the functional state of the joints must be maintained); physical rehabilitation, which should be focused on exercises that avoid passive movement—that can result in tissue inflammation leading to ossification—and exercises that help patients perform their daily activities. Intramuscular injections should be avoided as much as possible (subcutaneous injections and venipuncture do not represent the same risk). Dental care is also important; however, it is necessary to avoid keeping the mouth open for prolonged periods to prevent joint ankylosis. Removal of the tumors should be avoided, as it will cause a recurrence of heterotopic ossification foci and, thus, disease progression[17].

Interdisciplinary treatment by Pneumology (for evaluating lung function), Physical Medicine and Rehabilitation, Orthopedics, and Audiology services is important[17]. Due to the autosomal dominant inheritance pattern of this disease, the offspring's risk for an affected individual is 50% per gestational event regardless of the sex of the product. Although family cases are very infrequent, comprehensive genetic counseling should be offered, including planning and preventing complications in the pre-pregnancy stage since this kind of pregnancy is classified as a high obstetric risk. The patient should be advised on the offspring's risk of developing the disease and the obstetric risks (thromboembolism due to prolonged immobilization, respiratory distress due to restrictive lung disease, delivery complications due to pelvic

muscles' ossification, prematurity, and fetal distress)[17]. Some studies on diagnosis during pregnancy have reported shortening and medial deviation of the first metatarsal on structural ultrasound, leading to suspicion of this disease[18]. As no curative treatment currently exists, therapy is primarily directed at supportive measures such as those mentioned above. Non-steroidal anti-inflammatory drugs and corticosteroids are used to decrease excessive inflammation and control pain; some drugs such as bisphosphonates and leukotriene inhibitors are also used but with little efficacy[6]. Currently, therapies aimed at slowing the progression and preventing the formation of ossification foci are being developed[6]. In phase 2 clinical study, promising results have been shown: evidence showed a decrease in the size of heterotopic ossification foci and arrest of disease progression using a selective retinoic acid receptor gamma agonist (palovarotene)[19,20].

Manifestations of this condition are incapacitating and seriously affect the quality of life, for which a timely diagnosis is imperative to prevent situations that trigger ossification foci. In this case, comprehensive genetic counseling was provided, including a broad explanation of the condition's natural history. The patient and the family were made aware of the risks of recurrence for the parents of the index case (less than 1% because it is a *de novo* variant) and for the patient's offspring (50%). The patient started an interdisciplinary treatment that has been of great benefit to the patient.

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 patient data publication.

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 conflict of interest.

Funding

None.

Acknowledgments

We thank the family of the patient and all those who collaborated in the preparation of this work.

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