

Fibrodysplasia ossificans progressiva: diagnosis in primary care

Fibrodisplasia ossificante progressiva: diagnóstico em atenção primária

Fibrodisplasia osificante progresiva: diagnostico desde la atención primaria

Jesus Garcia-Pinzas¹, Jose Eduardo B. Wong², Miguel Angel P. Fernández³, María Angélica Rojas-Espinoza⁴

ABSTRACT

Objective: To show that it is possible to diagnose fibrodysplasia ossificans progressiva in the primary health care.

Case description: A 10-year-old female patient that has developed, since the age of 4, progressive stiffness of the joints and spine and ossification of soft tissues, often associated with trauma. The hallux valgus deviation of both toes was present from birth. X-ray showed the presence of heterotopic ossification.

Comments: This disease is likely to be diagnosed with the resources available in primary health care, since it is based on clinical findings. Currently, there is no cure for this disease, but high doses of corticosteroids and the use of nonsteroidal anti-inflammatory drugs, which are available in the primary care level, may limit the development of new calcifications and mitigate the pain, improving the quality of life of these patients.

Key-words: myositis ossificans; heterotopic ossification; primary health care.

RESUMO

Objetivo: Buscou-se demonstrar ser possível diagnosticar a fibrodysplasia ossificante progressiva na atenção primária à saúde.

Descrição do caso: Paciente de dez anos que, desde os quatro anos, mostrava rigidez progressiva nas articulações e na coluna vertebral, além de ossificações de partes moles, muitas vezes associadas a traumatismos. Havia desvio de

hálux valgo dos primeiros artelhos de ambos os pés, presente desde o nascimento. Por meio de radiografias, demonstrou-se a presença de ossificações heterotópicas.

Comentários: É possível realizar o diagnóstico desta doença com recursos disponíveis em atenção primária à saúde, uma vez que se baseia fundamentalmente em critérios clínicos. Atualmente, não existe cura para a doença, mas é possível limitar o desenvolvimento de novas calcificações, assim como mitigar a dor causada pelos recrudescimentos da doença, melhorando a qualidade de vida dos pacientes. Para isso, são utilizadas altas doses de corticoides e anti-inflamatórios não esteroides, disponíveis nos níveis primários de atenção.

Palavras-chave: miosite ossificante; ossificação heterotópica; atenção primária à saúde.

RESUMEN

Objetivo: Se buscó demostrar que es posible diagnosticar la Fibrodysplasia Osificante Progresiva (FOP) desde la atención primaria de Salud.

Descripción del Caso: Se describe el caso de una paciente de 10 años que desde los 4 años, desarrolla rigidez progresiva en las articulaciones y en la columna vertebral, además de osificaciones de partes blandas, muchas veces asociada con traumatismos; un rasgo importante fue la desviación en Hallux Valgus de los primeros dedos de ambos pies, presente desde su nacimiento; por medio de radiografías se demostró la presencia de osificaciones heterotópicas.

Comentarios: el diagnóstico de esta enfermedad es factible de realizarse con recursos disponibles en la Atención

Instituição: Universidad Nacional Hermilio Valdizán de Huánuco, Huánuco, Peru
¹Cirurgião do Posto de Saúde Chinchao, Red de Salud Huanuco, Universidad Nacional Hermilio Valdizán de Huánuco, Huánuco, Peru
²Pediatra do Centro de Salud Carlos Showing Ferrari, Huánuco, Peru
³Epidemiologista do Hospital II Salud Huánuco, Huánuco, Peru
⁴Estagiária de Medicina pela Universidad Nacional Hermilio Valdizán de Huánuco, Huánuco, Peru

Endereço para correspondência:
Jesús García-Pinzás
Jr. Mayro, 725
Huánuco – Peru
E-mail: jesgar2121@hotmail.com

Conflito de interesse: nada a declarar

Recebido em: 2/4/2012
Aprovado em: 11/9/2012

Primaria de Salud ya que se basa fundamentalmente en criterios clínicos. Actualmente no existe cura para esta enfermedad, pero es posible limitar el desarrollo de nuevas calcificaciones, y así como mitigar el dolor que causan las reagudizaciones de la enfermedad, mejorando la calidad de vida de los pacientes, utilizando para ello altas dosis de corticoides y antiinflamatorios no esteroideos, disponibles en el primer nivel de atención.

Palabras-clave: miositis osificante; osificación heterotópica; atención primaria de salud.

Introduction

In Peru and throughout Latin America, many medical professionals work in the Primary Health Care sector, i.e., provide “Essential care, based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community”⁽¹⁾. In this context, clinical skills are indispensable due to the lack of technological resources to support or rule out diagnostic suspicions. These very clinical skills are the ones that will help to fight against a disease as rare as Fibrodysplasia Ossificans Progressiva (FOP).

FOP was described for the first time by Guy Patin in 1693 (“the woman who turned into wood”), but it was only in 1736 that, in a communication to the Royal Society of Medicine in London, dr. John Freke described it in scientific terms, reporting the case of a 14-year-old male with swellings on his back⁽²⁾. In 1924, Noble proposed to divide the disease into three categories: myositis ossificans progressiva, myositis ossificans circumscripta progressiva, and myositis ossificans circumscripta. In 1969, Munchmeyer changed the designation to FOP, which encompasses the involvement of more soft tissues besides that of muscles^(2,3).

FOP is a rare condition of skeletal malformations such as bilateral hallux valgus and progressive heterotopic ossification of soft tissues; in other words, a new non-neoplastic bone is produced in places where it should not be, leading to permanent immobility throughout the years^(3,4). This disease is produced by a mutation in one of the copies of the gene that encodes the Receptor I of the bone morphogenetic protein, called Activin type 1 receptor or ACVR1⁽⁵⁾. It affects men and women equally, with a current worldwide prevalence of approximately 1 case in 2 million individuals^(4,6).

Case report

At a primary health care center in the Region of Huánuco (one of the poorest in Peru), a region characterized by essentially comprising a rural population living in poverty and extreme poverty, there was the case of a 10-year-old girl suffering from multiple swellings in her back along with progressive stiffness in the left elbow for approximately 6 months and complaining of severe pain, predominantly in the joints and back, especially at night. She points out that there was no previous history of a similar condition in her family, and the mother reported that her daughter was born at home and that the only remarkable event at the girl's birth was the presence of a bilateral deformity of both great toes, and then she had a “normal” growth and development until the age of 4, when she presented with painful, soft and mobile swellings in the neck that disappeared with time. Similarly, as years passed by, swellings appeared in her back, but they changed from being soft and mobile at

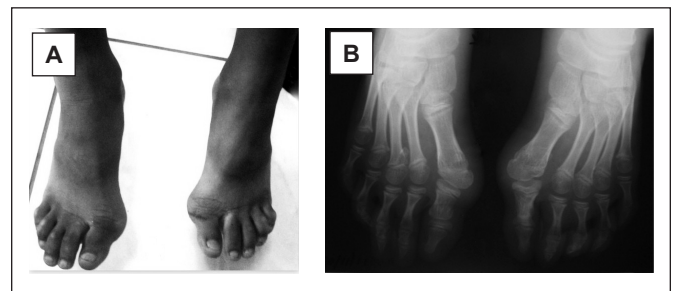


Figure 1 - A. Physical Evaluation. B. Radiographic image. Abnormal first metatarsal bone angulation, with an angle higher than 20 degrees in relation to first phalanxes, indicating bilateral hallux valgus. Radiopacity in the third metatarsal of the right foot

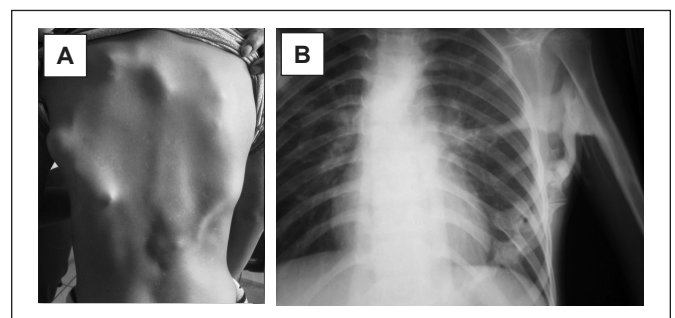


Figure 2 - A. Multiple painless and immovable swellings of stony consistency. B. Radiographic image (posteroanterior view) showing soft tissue heterotopic ossification, predominantly on the left side

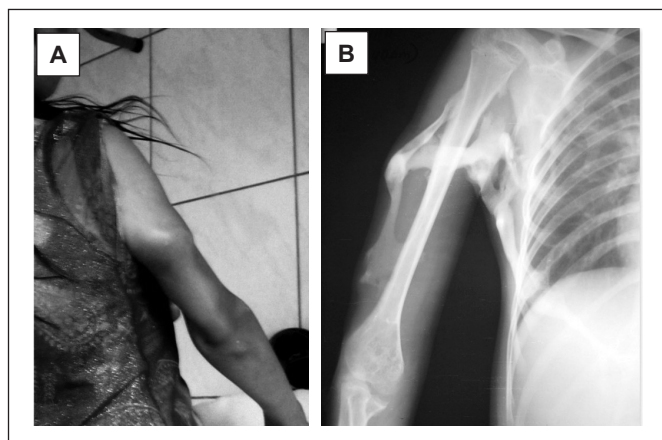


Figure 3 - Patient's right arm. A. Posterior view of the swelling. B. Extensive ossification of soft parts affecting the humerus and spreading out towards the right scapular region. Cortical thinning of the right distal humeral epiphysis, remarkable lytic lesions

the beginning to being hard and immobile, causing pain during their appearance, and some of them were associated with trauma.

Physical examination showed the presence of multiple asymmetric swellings in her back, which had a stony consistency, adhered to deep planes, were immobile and painless to palpation, and showed no inflammatory signs; an immobile and painless swelling of stony consistency and measuring nearly 10-cm long by 5-cm wide was also identified in the upper third of the right arm; an increase in volume and flexion stiffness in the left elbow joint was observed, causing pain when the patient attempted to perform active or passive movements; stiffness in the entire spine was also found, affecting from cervical to lumbar vertebrae and constituting a case of severe axial stiffness; her hands showed mild cubital deviation, particularly in the left hand; the shortening and deviation of both great toes were also worth of attention, constituting a case of bilateral hallux valgus; additionally, it was found that the patient had no fever or feeling of increased body temperature during the progress of the disease.

X-rays showed heterotopic calcifications, and laboratory tests such as blood cell count, C-reactive protein (PCR), rheumatoid factor, non-treponemal tests (RPR), and complete urine examination showed normal results, except for a mild eosinophilia, whose cause could not be determined. Considering these results, and analyzing the signs and symptoms presented by the patient, the clinical diagnosis of Fibrodysplasia Ossificans Progressiva was

confirmed. The management of the disease was started with the use of NSAIDs for the treatment of chronic pain and high doses of corticosteroids to limit the duration and the sequelae of disease flare-ups and exacerbations. At 6 month follow-up, it was observed that the patient's ranges of motion had improved, she moved with more confidence, her pain has been reduced, and her quality of life has improved.

Discussion

FOP is a genetic disease that in most cases is caused by a spontaneous new mutation in the *ACVR1* gene; in the remaining cases, it might have been inherited from one of the parents through a dominant autosomal pattern, since an affected patient has a 50% chance of having a child with FOP. This mutation causes a deregulation of the bone morphogenetic protein signaling pathway^(7,8). Previous studies have demonstrated that there was no ethnic, racial, gender or geographic predisposition for the development of the disease^(3,4). It is known that both genetic and environmental factors determine FOP phenotype, the first during prenatal development and the latter in the progression of heterotopic ossifications^(5,7,8).

During the course of the disease, according to what was described in cases reported worldwide⁽⁹⁻¹¹⁾ and to the analysis of the present case, FOP lesions may appear suddenly and cause severe inflammation within few hours. If a biopsy is performed in the early lesion, it could be confounded with several types of cancer, because a new bone is being formed through an endochondral process with massive cell proliferation^(7,8). It should make it clear that, if a biopsy is performed in a healing fracture, it would show exactly the same images, which would make one think of cancer if not aware of what is being observed. A careful retrospective analysis reveals that FOP lesions grow much faster than any cancer would do⁽⁸⁾.

Because FOP diagnosis is made clinically, it is possible to establish it in the primary health care setting, based on the clinical features that define the disease: malformation of the great toes and progressive heterotopic ossification^(3,4,6,9-11). Individuals with FOP appear normal at birth except for the characteristic malformation of the great toes^(3,4,10,11), which was noticed by the parents of the girl reported in the present study, but they did not pay much attention to this, since it did not cause functional changes.

This malformation was reported in almost all newborns affected by FOP, meaning that congenital hallux valgus malformation is the earliest and most typical phenotypic characteristic^(3,4,9). Ossification occurs in exacerbations of the disease, i.e., heterotopic ossification is manifested by the appearance of large and painful swellings of highly vascularized fibroproliferative tissue, often associated with trauma. These swellings begin to appear during the first decade of life, at 4 years on average^(10,11), coinciding with what was observed in the present case; children with FOP develop swellings formed from connective soft tissue, including fascia, ligaments, tendons, and skeletal muscle. These swellings progress until being ossified, firstly and typically affecting neck and upper back, making them stiff^(4,9,12); in the case that motivated this report, axial stiffness was the first functional change experienced by the patient.

According to what has been presented and to reports from other investigators, joint malformations and soft tissue ossification are the characteristic radiographic features of FOP. Malformations of great toes and cervical spine, along with the presence of tibial osteochondromas, help to confirm the diagnosis⁽⁹⁾. As for laboratory analysis, biochemical values are usually found to be normal, but it is possible to observe an increase in alkaline phosphatase activity during heterotopic ossification flare-ups^(4,9). The incidence of fractures is not increased in patients with FOP, although fracture healing is characteristically accelerated in heterotopic bone⁽⁸⁾. Several skeletal muscles, including the diaphragm, tongue, and extra-ocular muscles are enigmatically spared from FOP. Cardiac muscle and smooth muscle are not classically involved in the process of FOP⁽¹³⁾.

It is important to take into account and inform the patients suffering from this disease that minor trauma such as intramuscular immunizations, mandibular blocks, muscular trauma, falls, or colds could trigger a new episode of inflammatory swellings that will result in the ossification of these soft tissues (disease flare-up)^(4,14). Surgical attempts to obtain samples using biopsy or to remove a heterotopic bone could lead to episodes of explosive bone growth, which could be even much more severe than those caused by disease flare-ups⁽¹⁴⁾. Therefore, it is necessary to control the environment of affected people, preventing, whenever possible, their exposure to situations that could exacerbate the disease, as well as avoiding invasive procedures in case of suspected FOP, which constitutes actions of primary care that can be performed in the primary health care level.

As for treatment, there are anecdotal reports on the efficacy of corticoids in limiting inflammation and progression of heterotopic ossification during flare-ups, which means that if prednisone is administered at a 2mg/Kg/d dose during 4 days, starting within the first 24 hours after the flare-up, the intense inflammation and tissular edema observed in the first stages of ossification will be reduced. When prednisone is discontinued, a NSAID or a cox-2 inhibitor can be used for the symptomatic treatment of the flare-up and the pain^(4,12). These therapeutic elements are available in most primary health care establishments; therefore, the management of the disease and the prevention of major sequelae can be implemented in this level.

The diagnosis of this disease usually goes unnoticed due to the fact that it is often diagnosed incorrectly, including in high level centers; it is reported that this entity is commonly misdiagnosed as cancer, fibromatosis, ossifying hematomas, or even scleroderma^(6,9,13). Delayed and incorrect diagnosis cause much pain and suffering for patients and their families throughout the world, besides usually worsening their clinical picture⁽¹³⁾. Therefore, it is extremely important to suspect of this diagnosis since the first contact with patients presenting these features. Although there are confirmatory genetic tests for the mutation responsible for the disease, they are not available in primary health care; in fact, several Latin American countries do not have these tests available. These circumstances should not limit nor delay the management of the disease, since it was demonstrated that FOP diagnosis is essentially clinical.

Although it is known that bone formation in FOP is episodic, the disability it produces is cumulative, confining patients to a wheelchair by the third decade of life, and stiffness makes them dependent on assistance in performing activities of daily living. Many of them will experience severe weight loss resulting from ankylosis of the jaw and might develop pneumonia or heart failure as a result of chest wall stiffness, thus their survival is approximately 45 years, and death often results from complications of thoracic insufficiency syndrome⁽¹⁵⁾.

Finally, it is important to intervene in the development of this disease, due to the disability it causes for the affected patients and the burden it represents to their families and the society, which is possible to be done in the primary health care setting, since the definite diagnosis can be made by clinical evaluation^(4,9) that associates progressively ossifying soft tissue lesions with malformation of the great toes.

References

1. World Health Organization [homepage on the Internet]. Declaration of Alma-Ata. Proceedings of International Conference on Primary Health Care; 1978 Sep 6-12; Alma, Ata, USSR [cited 10 Nov 2011]. Available from: http://www.who.int/publications/almaata_declaration_en.pdf
2. Kaplan FS. Fibrodysplasia ossificans progressiva: an historical perspective. *Clin Rev Bone Mineral Metab* 2005;3:179-82.
3. Connor JM, Evans DA. Fibrodysplasia ossificans progressiva. The clinical features and natural history of 34 patients. *J Bone Joint Surg Br* 1982;64:76-83.
4. Kaplan FS, Le Merrer M, Glaser DL, Pignolo RJ, Goldsby RE, Kitterman JA *et al*. Fibrodysplasia ossificans progressiva. *Best Pract Res Clin Rheumatol* 2008;22:191-205.
5. Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L *et al*. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. *Hum Mutat* 2009;30:379-90.
6. Sferco A. Fibrodysplasia osificante progresiva: pautas para su reconocimiento. *Arch Argent Pediatr* 2001;99:249-52.
7. Shore EM. Fibrodysplasia ossificans progressiva (FOP): A human genetic disorder of extra-skeletal bone formation, or -How does one tissue become another? *Wiley Interdiscip Rev Dev Biol* 2012;1:153-65.
8. Shafritz AB, Shore EM, Gannon FH, Zasloff MA, Taub R, Muenke M *et al*. Overexpression of an osteogenic morphogen in fibrodysplasia ossificans progressiva. *N Engl J Med* 1996;335:555-61.
9. Kaplan FS, Xu M, Glaser DL, Collins F, Connor M, Kitterman J *et al*. Early diagnosis of fibrodysplasia ossificans progressiva. *Pediatrics* 2008;121:e1295-300.
10. Gonçalves AL, Masruha MR, de Campos CC, Delai PL, Vilanova LC. Fibrodysplasia ossificans progressiva: case report. *Arq Neuropsiquiatr* 2005;63:1090-3.
11. Forero Melo JF, Vargas Bazurdo MC, Alarcón F. Fibrodysplasia Osificante progresiva: reporte de caso. *Rev Colomb Radiol* 2011;22:3113-6.
12. Kaplan FS, Shore EM, Pignolo RJ. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. *Clin Proc Intl Clin Consort FOP* 2011;4:1-100.
13. Saldivar AC, Cruz BC. Fibrodysplasia osificante progresiva. Reporte de un caso y revisión de la Bibliografía. *Med Int Mex* 2009;25:245-7.
14. Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. *Pediatrics* 2005;116:e654-61.
15. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am* 2010;92:686-91.