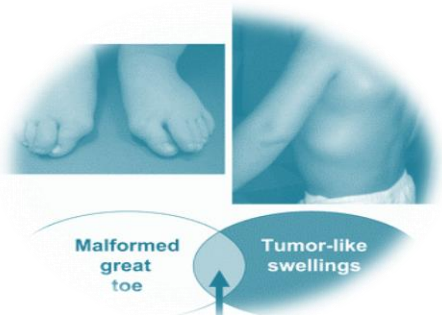


CME on Fibrodysplasia Ossificans Progressiva (FOP)

Objectives

Upon completion of the program, the learners are expected to

- Be aware that great toe malformations and soft tissue swellings are the diagnostic signs of FOP.
- Recognize that tumor is the most common misdiagnosis of FOP and biopsy can cause harm.
- Diagnose, manage, and treat FOP in the era of disease specific therapy is available.

Faculty

- Christiaan Scott, MBChB

  Professor, Department of Pediatrics, University of Ottawa, Canada and Hon. Professor Pediatrics University of Cape Town, South Africa

- Michelle Davis

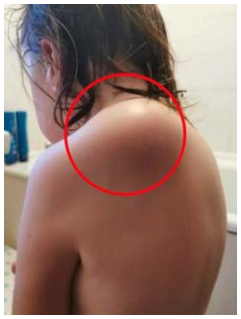
  Executive Director, International Fibrodysplasia Ossificans Progressiva Association (IFOPA)

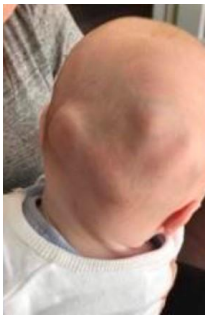
Faculty Presentation

Christiaan Scott, MBChB

What is fibrodysplasia ossificans progressive (FOP)

There are some simple messages that will help you to diagnose this rare condition. What do you do when a young lady such as this one walks into your office with a large swelling over her back or neck, or a young baby in the first year of life comes to you with swellings at the back of his or her head. You'd be well forgiven for being concerned about cancer or some other malignant process, or an infective process or something else, and you'd be forgiven for thinking you'd need to refer to surgery for a biopsy, or to oncology for further workup, or get an MRI?





Photos courtesy of Tin Soldiers
FOP Diagnostic Handbook

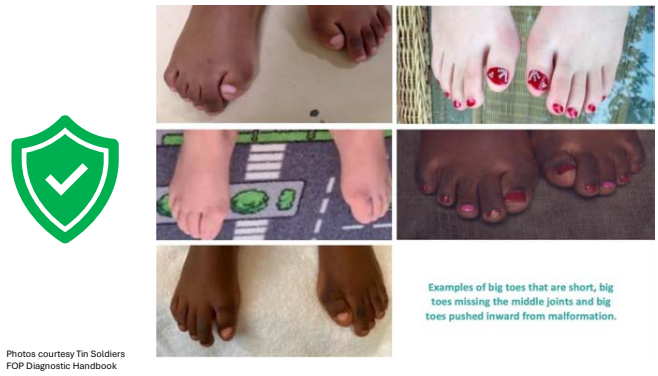
Well, we all have sworn to first do no harm when people come in to see us for medical diagnosis, procedures, and treatment. Here's an opportunity to avoid doing harm, because most of the things about further investigating are things that will actually cause harm to these children. Even though we intend to help these patients with these procedures, in this case, it turns out that they're contraindicated.

These children presented with early signs of a condition known as fibrodysplasia ossificans progressiva. This is a disease which starts in early childhood. It's characterized by the development of bone forming in parts of the body where bone shouldn't be forming. So all muscles and connective tissues in the musculoskeletal system eventually become replaced by bone, leading to a body being trapped. As you can see in these dramatic pictures

an encasing second skeleton of bone. That's where the name comes from. It starts with this dysplasia, and it develops progressively as ossification outside of the skeleton. It locks people into this skeleton. It's a devastating condition.

Can we identify patients with FOP from malformed toes and tumor-like swellings?

I'd like to say the diagnosis is easy. At the same time, misdiagnosis is very harmful. So how do you make this diagnosis? Well, when that girl or that young boy comes into your office with the lumps on their back, head or neck, the only thing you have to do, or the first thing you have to remember is to look at their toes.



Photos courtesy Tin Soldiers FOP Diagnostic Handbook

All people with FOP are born with malformed first toes. The toes are in a valgus position, they might miss the first joint, i.e. there may be no flexibility to the toe at all. They will often be shortened and deviated. When you see this combination of features of outward pointing, shortened non-bending toes, combined with lumps that start on the back of the neck or the back of the head, and sometimes other parts of the body, you need to consider the diagnosis of FOP.

While children can have malformed toes for other reasons, such as isolated congenital malformations or juvenile bunions, or people might have tumor like swellings on their backs from other reasons such as sarcomas and desmoid tumors and other reasons, it's unusual, or it's very specific when children get both of these two things together. A clinical diagnosis of FOP can easily be considered in this setting.

It's so easy, in fact, that I was paging through a book that belonged to my grandfather that was published in the late 19th century, and in here I saw this picture of the ossified man. The book was called *The Anomalies and Curiosities of Medicine*. In this book I was able to identify this man with FOP just by looking at the clinical description and even just by looking at the carefully made drawings of his toes that I've highlighted in this picture.

What is the reason for NOT performing a biopsy on the tumor-like swelling?

What is the reason for not wanting to do biopsies on these people with FOP when they present to your office? Why is it so important to recognize this condition by looking at these swellings and the abnormal toes before any surgical interventions are done?

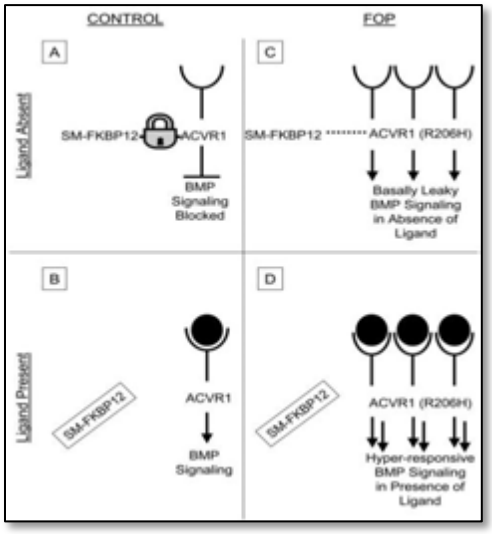
The reason is that when one cuts into muscle and causes injury to muscle in those areas, the ossification that was destined to happen in the tissues over a long period of time is accelerated and now starts to happen immediately while the body is trying to replace this injured and dying muscle from the surgical incision, it actually ends up replacing all of this muscle with bone. That's why surgery is completely contraindicated.

Similarly, mandibular blocks or intramuscular injections are contraindicated. Mandibular blocks for dental procedures can cause damage to the masseter muscle, and this can cause ossification of that muscle with profound clinical implications, as I'll show you in the next slide. The same can be said for intramuscular injections. Injections that go into the thigh can cause damage to the muscle there leading to necrosis of the muscle cells. When these muscle cells are being repaired and replaced, they're being repaired and replaced by bone. By doing one of those two procedures, you can take a child who's

happily munching on a hamburger to the point that within days or weeks have their jaw lock up to the extent where they'll never, ever do that again. The same with a child who's running and playing happily, if you injure the muscle in the thigh by virtue of intramuscular injections, you could be confining that child to a wheelchair earlier than it would have otherwise happened during the course of FOP.

What is the disease mechanism of FOP?

Why does this happen? What's the pathophysiology behind this? Well, one of the clues is that the progression of the ossification that we see in FOP develops according to the same pattern that our bodies have designed to make our first skeleton. In a way, the body is trying to build a second skeleton, but it's doing it on the blueprint exactly the same way as it had the first skeleton, which means it starts at the back and the neck, which is why that is where the lumps first appear. It develops upwards, downwards, and outwards as the child or adolescent ages, and their activity is regulated in turn by a protein called ACVR1 or LRRK2. It's mutations in ACVR1 or LRRK2 that cause this dysregulation of this process.



Kaplan and Shore, JBMM 2008

There you can see a schematic description of what happens. In normal people or people without FOP, they're labelled as control. ACVR1, which acts as a lock on the BMP receptor, prevents the BMP receptor from being activated. In people with FOP as shown in block number C, you can see there are more receptors and the ACVR1 lock is broken and therefore there is more expression of BMP. You can see how that lock generally would come off in a healthy person without FOP, the lock would come off when there's a need to build new skeleton. But in FOP, that lock is permanently broken. So there's this drive towards building new bone the whole time. This process is obviously more complicated than that. This diagram just shows you from the tissue level to the bone level and the intracellular level where all the steps are in the process.

Here you see that numerous therapies are being developed that target various parts of this pathway, from the initial inflammatory cells and mast cells that are involved, right down to gene expression and cartilage formation. There are drugs being designed targeting specific steps in this pathway.

What is the FOP clinical picture

At birth you get these. You can get these scalp nodules and malformed toes. Generally, in the first decade, children start to develop these lumps on their back and neck, as we saw with our first two patients. After that, they can develop a harder bone that forms and replaces these initially soft swellings. This can fix the spine into a scoliosis shape by the second decade of life. Usually, arms and legs become involved. This affects profoundly the mobility of people. By the third decade of life, most people have ankylosis of most of their joints due to heterotopic bone having formed around most of the other joints.

What are the complications of FOP

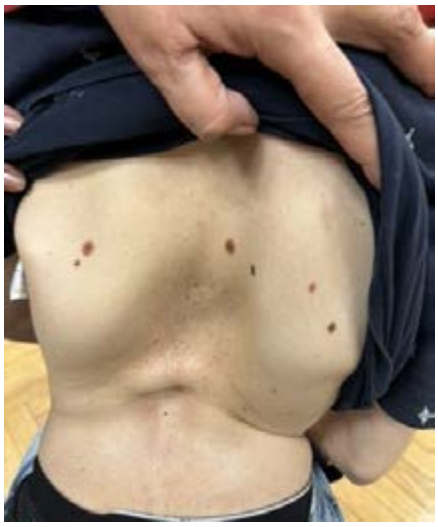


Photo courtesy of C Scott

What are some of the complications of FOP? I mentioned scoliosis in the beginning. As the bone forms, it can restrict the growth of the spine and cause scoliosis. This scoliosis and restriction of the chest wall can cause restrictive lung disease. The lung doesn't have space to expand and therefore becomes restricted. People can develop pneumonia as a result of the disordered lung function. They can develop other respiratory complications. Jaw ankylosis, as I mentioned earlier, is a terrible complication and people lose the ability to open their mouth. This has profound effects on their dental well-being, their dietary well-being, their quality of life.

Then people can also develop falls and fractures. People with FOP are not able to walk with ease, especially later in life. When they fall, they're also not able to lift up their arms to protect themselves and provide protective maneuvers. So falls can be devastating. Something such as a simple trip, which you and I would recover from instantaneously, someone with FOP is not able to recover, not able to protect themselves, and therefore are at high risk of getting seriously injured.

Here is a picture of a child from South Africa with FOP. You can see that her arms, even at her young age, are completely locked in that position. You can also get the impression that her lungs are restricted. You can see how small her chest wall is compared to the rest of her body. You can just imagine the restrictive lung disease that this beautiful child has.

This is a young man from our clinic. You can see he wears a helmet. Not always willingly, but this helmet is there because his arms are locked in position, and when he falls, he has no way of protecting his head. So the helmet provides him with some protection against falling.

This picture shows some of the life course of FOP. These are all people from South Africa with FOP. You can see the youngsters are still able to run around, even though they may have affected necks and arms, but the adults are by now wheelchair bound.

Photo courtesy of C Scott

What is the mortality of FOP

People with FOP tend to die younger than people with FOP. The majority of people from this study, which is a little bit outdated now, but it's the only study we have, shows that most people die of cardiorespiratory failure, pneumonia, falls, sepsis, or complications of general anesthesia. Remember that people with FOP have a limited mouth opening, they have limited neck movement, and so anesthesia is a particularly risky time, and anesthetic should

never be attempted in people with FOP without the requisite expertise being brought in, usually from outside of major specialist centers.

How to care for FOP patients

Caring for FOP starts with diagnosis. The value of the patient support system cannot be overstated. The international FOP Association (IFOPA) plays the most critical role. It acts as a central place where people with FOP can be supported in every way conceivable for the management of their FOP. As you can imagine, it's a devastating condition for people to be diagnosed with. To have IFOPA available to direct people, support them, direct them to the correct resources, and provide their loved ones with the best possible life with FOP is absolutely critical.

Part of that support is providing insight and direction in care for things like dentistry, which is critical for looking after the wellbeing of people with FOP, anesthesia management as I mentioned, and audiology screening. Most people with FOP develop hearing problems from early on in life, and this can be addressed early and can lead to better outcomes in terms of language and development and quality of life. Lung health is, as I mentioned, is a critical area of importance.

There are more things that can be done. Occupational therapists can help with physical aids as limbs become more restricted. There are innovative ways of allowing people to achieve their activities of daily living in a way that provides them with dignity and independence. The physical aids and a whole range of training around physical aids are available through the IFOPA website and through the skilled providers. It's critical, and it's the reason for giving this talk, to avoid harm through biopsies, injections, non-essential surgeries, etc. and also to provide mobility support for people with FOP. You can imagine with all of the talk of falling and moving around, it is devastating in its impact on mobility. Providing support to be able to get the right kind of wheelchair, usually motorized wheelchair is absolutely critical.

What is the treatment for FOP

We're at a very exciting time in the development of medications for FOP. There have been no really effective therapies for FOP, but that landscape is rapidly changing, with a number of new therapies on the horizon and one that's just been registered, as well as several clinical trials in development. There's also the need to treat flare ups. These bone-forming flare ups are a critical part of FOP.

I'll just mention the one drug that has been approved by the FDA and in Canada for the treatment of FOP in children older than eight. This is an RAR gamma antagonist called Palovarotene. It stops the change of a cartilaginous legion into an osteogenic legion. It doesn't completely stop the development of bone formation, but it did meet sufficient criteria for the FDA and the Canadian and some other health authorities to approve it as the first official therapy for FOP. The landscape is changing rapidly, there are a number of drugs here that I won't go through that are being considered, or that are in late phase clinical trials for the management of FOP.

The management of FOP is complex. It's impossible to remember all of this if you don't have a patient of your own with FOP. The one thing to remember is that you can always find the up-to-date management guidelines for FOP on the International Clinical Council on Fibrodysplasia Ossificans Progressiva’s website. I've given you the website address there. It's also available through the IFOPA website. Here you'll find comprehensive guidelines for every aspect of clinical care, including off label treatments and non-medical and non-pharmaceutical management of FOP.

Why does it matter to you as a clinician

So why does this matter to you as a clinician who's seeing patients with all kinds of other diseases?

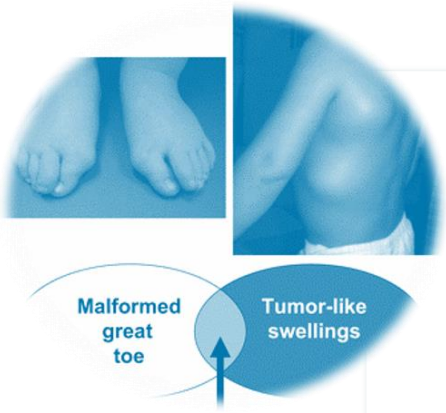
Well, not all the children with FOP in the world have been identified, and it's likely that one of you is going to see a patient with FOP at some point. When you do or when you're asked to consult on someone with lumps on their back or malformed toes, I want you to remember this talk and be able to direct therapy in a way that doesn't cause harm to the child. That's the first and most important step.

The second is that treatments are on the horizon and a first treatment has even been registered in Canada and USA. There are several clinical trials enrolling all over the world. So no matter where you are, it's possible that you might be able to diagnose a patient who could then participate in the clinical trial.

This CME program is provided by P2P Syncro, Partners for Advancing Clinical Education, International Fibrodysplasia Ossificans Progressiva Association (IFOPA). It is supported by an independent medical educational grant from Ipsen Pharmaceuticals.

Faculty Disclosure: Christiaan Scott: Consultant/Advisor/Speaker: Ipsen Pharmaceuticals in the past 24 months. Michelle Davis: Nothing to disclose.

Transcript edited for clarity and brevity.

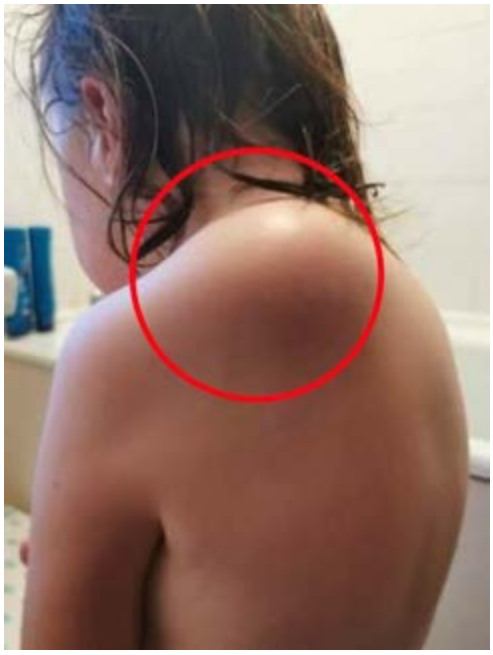


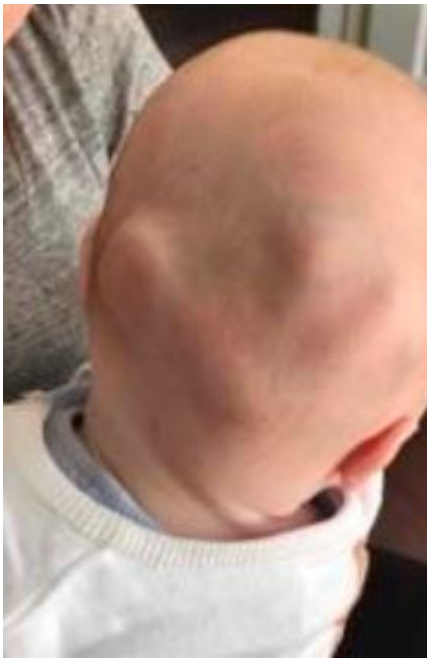
Fibrodysplasia Ossificans Progressiva (FOP)

CME

Christiaan Scott, MBChB
Michelle Davis

2024-2025



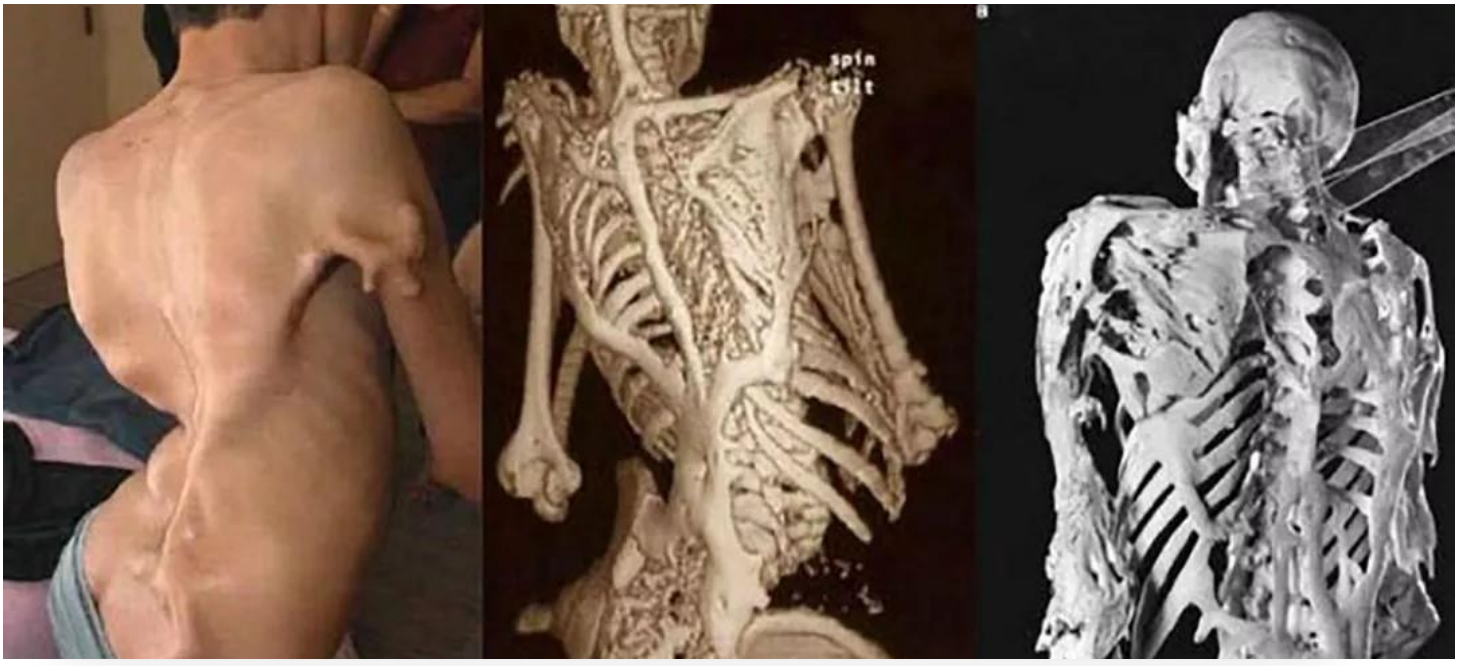


Photos courtesy of Tin Soldiers FOP Diagnostic Handbook

First

Do No Harm

CME faculty C Scott



Fibrodysplasia Ossificans Progressiva

Photos courtesy Kaplan et al

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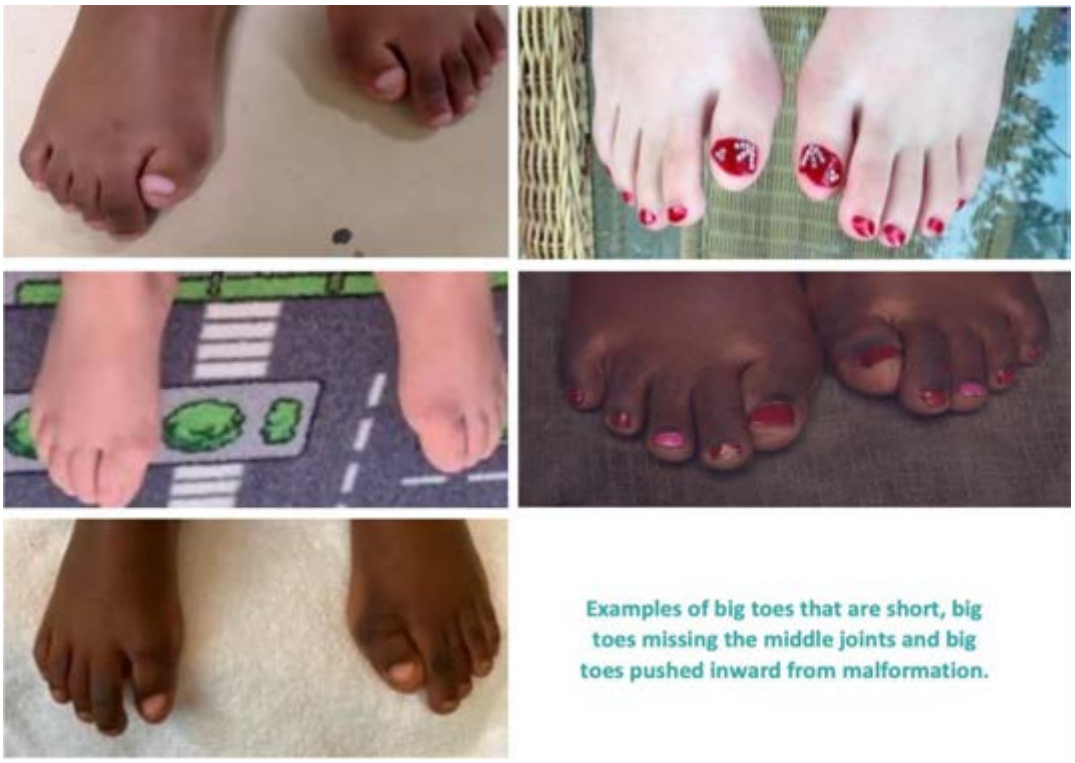
Diagnosis is Easy

Misdiagnosis is harmful

CME faculty C Scott



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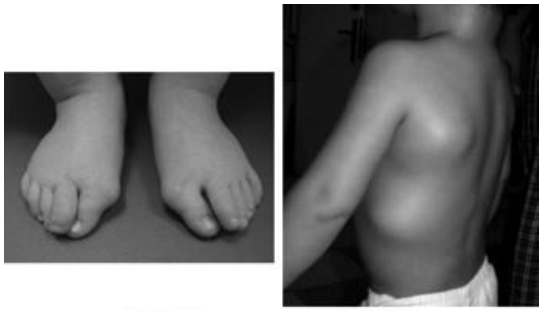
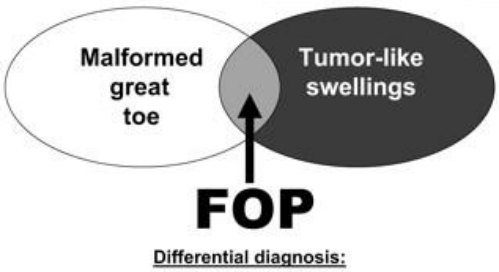


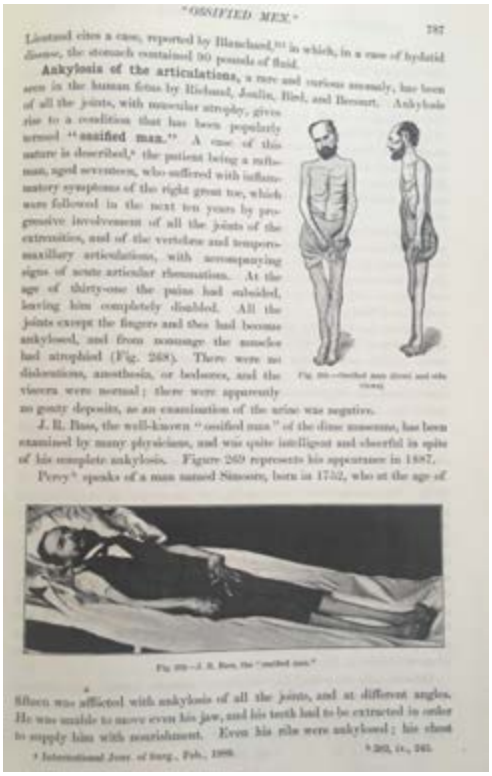


Differential diagnosis:

- Isolated congenital malformations
- Brachydactyly (isolated)
- Juvenile bunions
- Sarcoma
- Desmoid tumor
- Aggressive juvenile fibromatosis
- Lymphedema

Photos Kaplan et al and Chris Scott

CME faculty C Scott



"OSSIFIED MEN." 787

Liestand cites a case, reported by Blanchard,[21] in which, in a case of hydatid disease, the stomach contained 80 pounds of fluid.

Ankylosis of the articulations, a rare and curious anomaly, has been seen in the human fetus by Richard, Joulin, Bird, and Bernutz. Ankylosis of all the joints, with muscular atrophy, gives rise to a condition that has been popularly termed "**ossified man.**" A case of this nature is described,* the patient being a salesman, aged seventeen, who suffered with inflammatory symptoms of the right great toe, which were followed in the next ten years by progressive involvement of all the joints of the extremities, and of the vertebræ and temporo-maxillary articulations, with accompanying signs of acute articular rheumatism. At the age of thirty-one the pains had subsided, leaving him completely disabled. All the joints except the fingers and toes had become ankylosed, and from nonusage the muscles had atrophied (Fig. 268). There were no dislocations, anæsthesia, or bedsores, and the viscera were normal; there were apparently no gouty deposits, as an examination of the urine was negative.

J. B. Bass, the well-known "ossified man" of the dime museums, has been examined by many physicians, and was quite intelligent and cheerful in spite of his complete ankylosis. Figure 269 represents his appearance in 1887.

Percy* speaks of a man named Simons, born in 1752, who at the age of fifteen was afflicted with ankylosis of all the joints, and at different angles. He was unable to move even his jaw, and his teeth had to be extracted in order to supply him with nourishment. Even his ribs were ankylosed; his chest

* International Journ. of Surg., Feb., 1888. † 262, ix., 245.

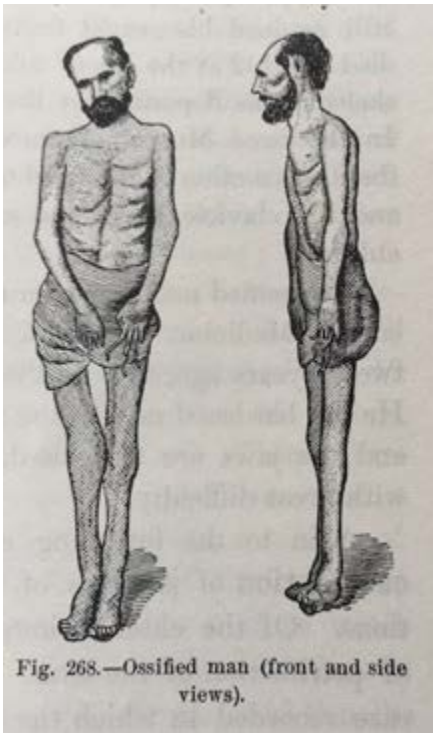
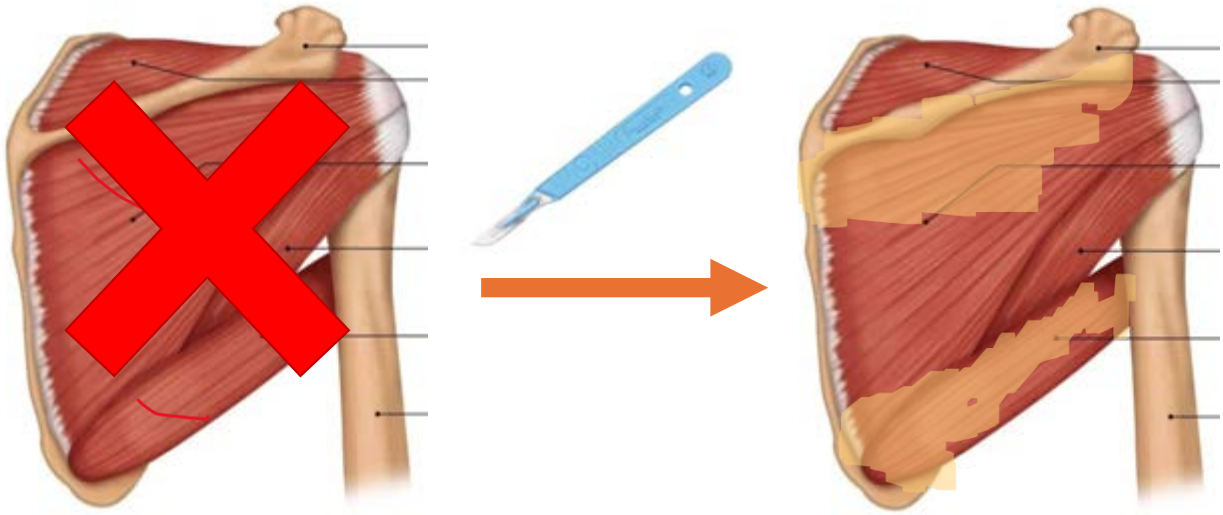


Fig. 268.—Ossified man (front and side views).

CME faculty C Scott

DO NOT BIOPSY FOP



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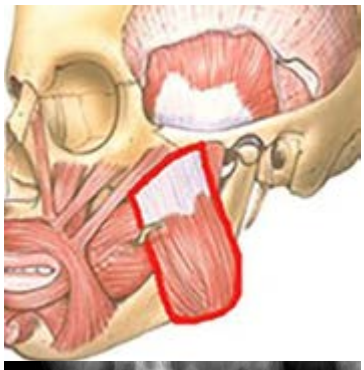
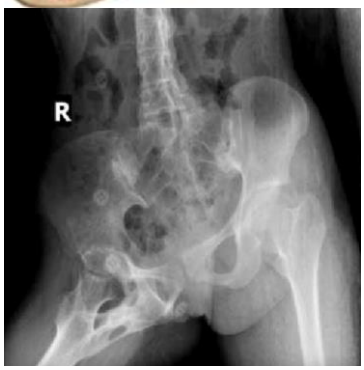
Schoenmaker et al, Frontiers, 2022



Mandibular Blocks

Intramuscular Injections

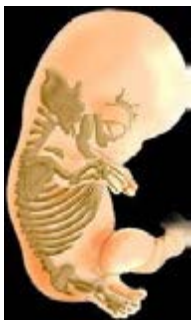


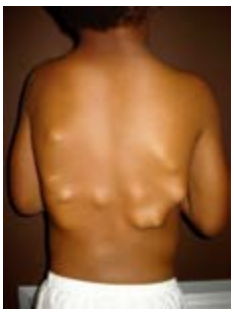
Dhamangaonkar et al, JOS, 2013

CME faculty C Scott

CME faculty C Scott

Embryonal Progression of Ossification





BMPs have an important role in *embryonic patterning* and early skeletal formation

BMP4 help regulate polarity of the embryo (i.e. back to front patterning)

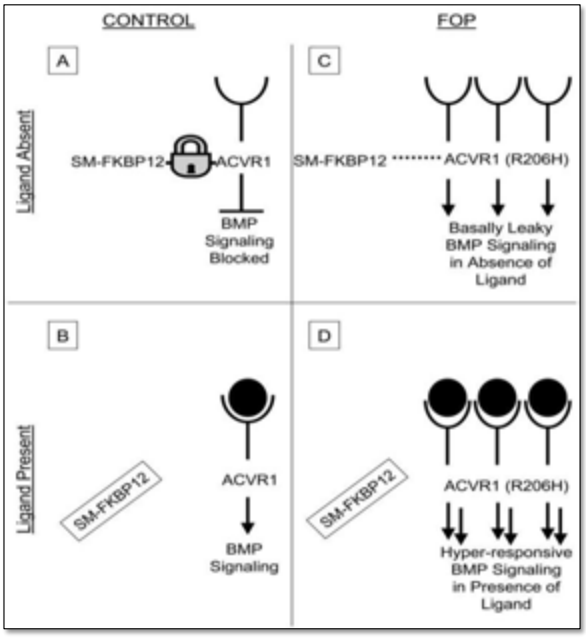
ACVR1/ALK2 regulates BMP activity

A missense mutation of ACVR 1 causes FOP

Photo courtesy of C Scott

CME faculty C Scott

Proposed role of ACVR1 and BMP



Kaplan , Shore , JBMM 2008

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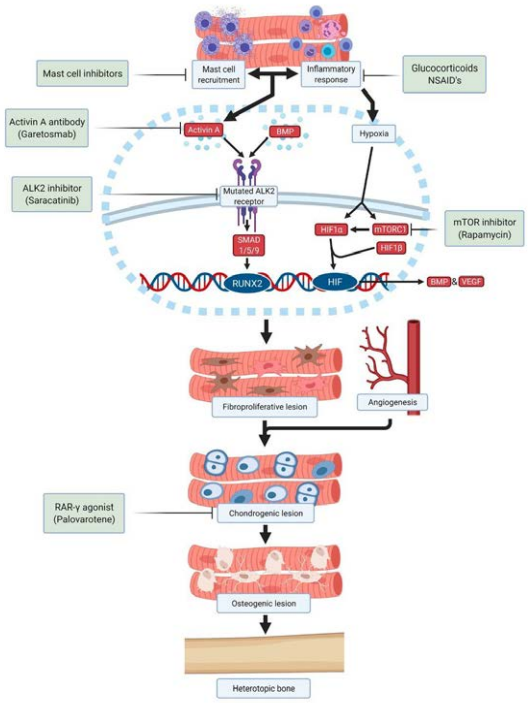

De Ruiter, Endo, 2021

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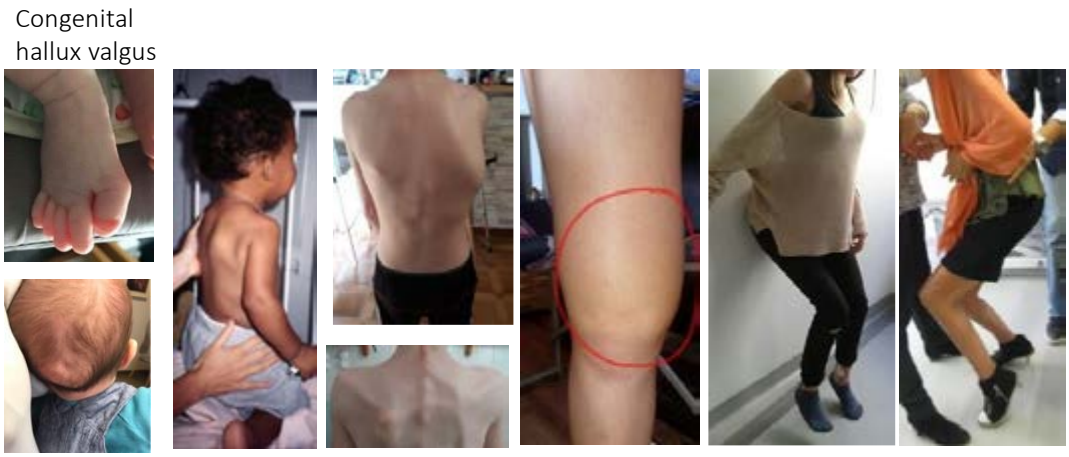
FOP Classical Clinical Features



Photos courtesy of Tin Soldiers FOP diagnostic Handbook

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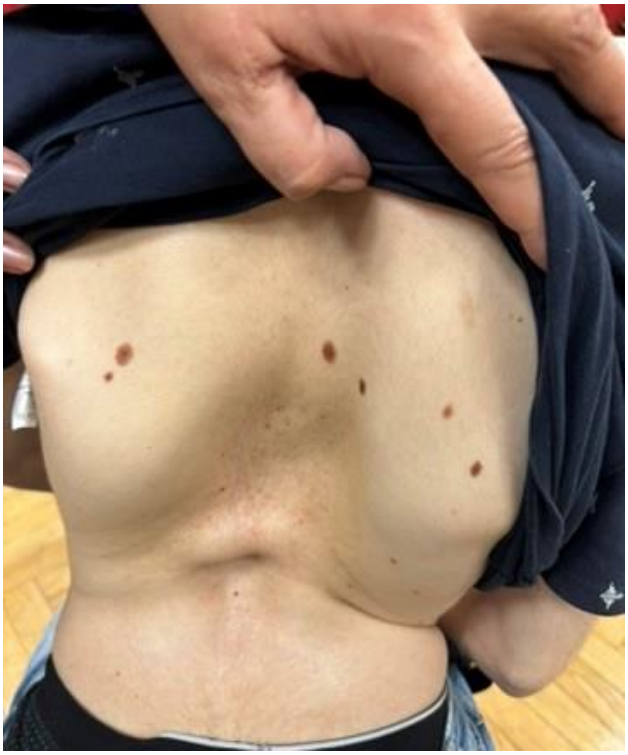

Common Complications of FOP

- Scoliosis
- Restrictive Lung Disease
- Pneumonia
- Respiratory complications
- Jaw Ankylosis
- Dental Problems
- Falls
- Fractures

Photo courtesy of C Scott

CME faculty C Scott

Photo courtesy of C Scott

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Early Mortality and Cardiorespiratory Failure in Patients with Fibrodysplasia Ossificans Progressiva

By Frederick S. Kaplan, MD, Michael A. Zasloff, MD, PhD, Joseph A. Kitterman, MD, Eileen M. Shore, PhD, Charles C. Hong, MD, PhD, and David M. Rocke, PhD

Investigation performed at the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

TABLE I Causes of Mortality in Patients with Fibrodysplasia Ossificans Progressiva

Cause	No.	Percentage	M	F	Age Range *(yr)*	Median Lifespan *(yr)*
Cardiorespiratory failure	26	54	12	14	8-58	42
Pneumonia	7	15	3	4	28-60	40
Falls	5	11	2	3	32-46	41
Sepsis	3	6	3	0	46-56	52
Complications of general anesthesia	2	4	0	2	12-15	14
Intestinal obstruction	1	2	1	0	28	28
Starvation	1	2	1	0	15	15
Drowning	1	2	0	1	3	3
Accident	1	2	1	0	25	25
Suicide	1	2	1	0	30	30
Total	48	100	24	24	3-60	40

CME faculty C Scott

Caring for FOP starts **with a Diagnosis**

Patient Support

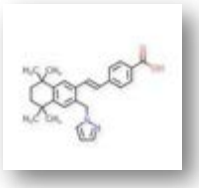
ifopa
INTERNATIONAL FIBRODYSPLASIA OSSIFICANS PROGRESSIVA ASSOCIATION

Preventing complications

Dentistry
Anesthesia
Audiology
Lung health

Medical treatment

New therapies
Clinical Trials
Treating flare ups



Physical Aids

Avoiding Harm

Biopsies
Injections
Non-essential surgeries
Mobility support

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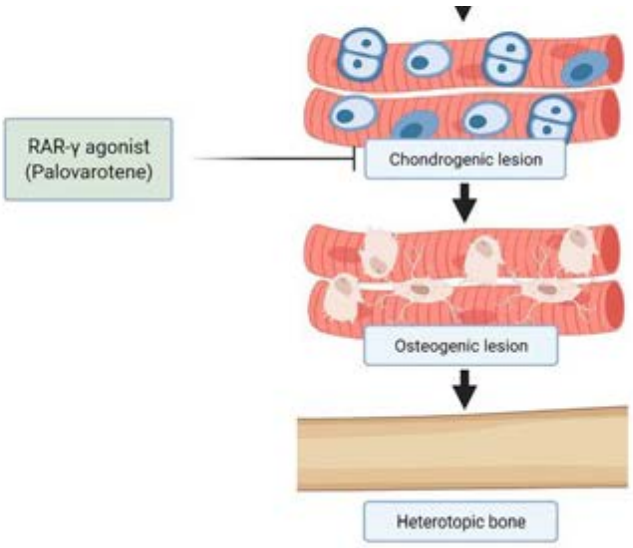

De Ruiter, Endo, 2021

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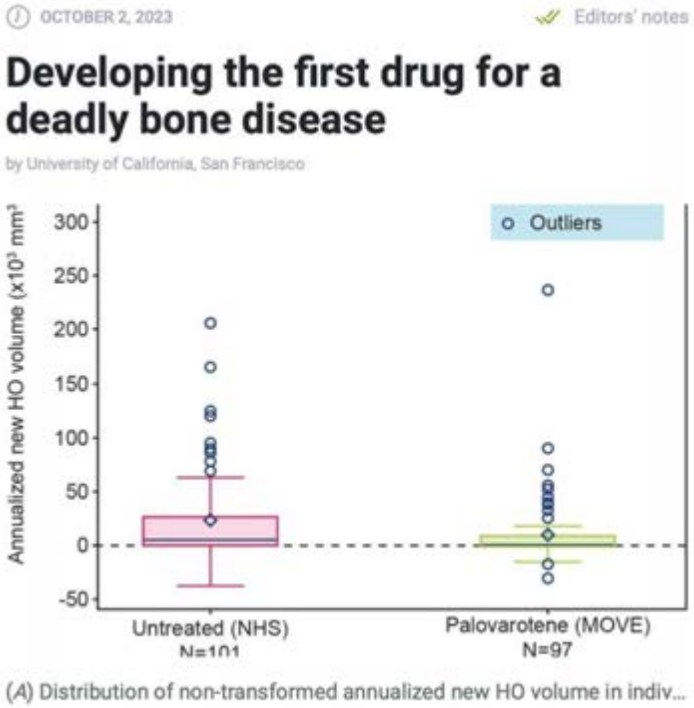

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FOP Drug Development

Drug	Mechanism	Proponent	Discovery	Pre-Clinical	Clinical Phase 1 2 3	Approval
Palovarotene	RARγ Agonist	Ipsen				
Rapamycin	Immune Suppression	Kyoto University				
REGN2477	Activin A mAb	Regeneron				
Saracatinib	ALK2 Inhibition	Vumc/Oxford/Harvard				
BCX9250	ALK2 Inhibition	BioCryst				
BLU-782	ALK2 Inhibition	Ipsen				
Kinase Inhibitor	ALK2 Inhibition	Keros				
ALK2 Antibody	Anti-ALK2 Receptor mAb	Daiichi Sankyo/Saitama				
ALK2 Antibody	Anti-ALK2 Receptor mAb	Navrogen				
Allosteric Inhibition	ALK2 allosteric Inhibition	Oxford/M4K Pharma				
Antisense Oligo	↓ ACVR1 allele expression	University of Alberta				
Senotherapeutics	Senescent cell clearance	Mayo Clinic				
BYL719	PI3Kα Inhibition	University of Barcelona				
H-SAADD	ALK2 Degradation	Texas A&M University				
Kinase Inhibitor	ALK2 Inhibition	La Jolla/ Emory University				
TAK1 Inhibitor	Kinase inhibitor	University of Michigan				

From Pignolo, Kaplan exp opinion orphan drugs, 2020

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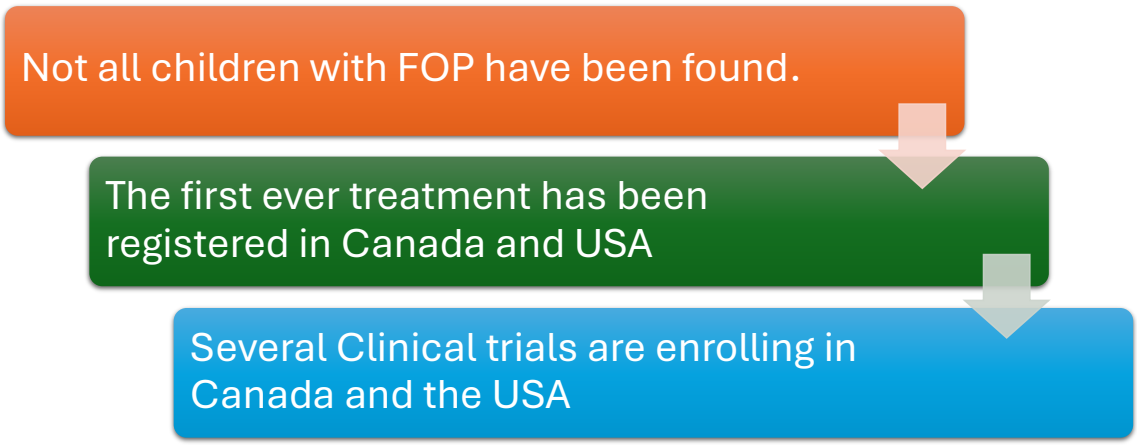
Why Does It Matter to You



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