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CASE BASED REVIEW

Challenges in the treatment of fibrodysplasia ossificans progressiva

Kardelen Gencer-Atalay[1] · Ekim Can Ozturk[1] · Ilker Yagci[1] · Pinar Ata[2] · Kenan Delil[2] · Zerrin Ozgen[3] · Gulseren Akyuz[1]

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Abstract

Fibrodysplasia ossificans progressiva (FOP), is a rare autosomal dominant connective tissue disease with a prevalence of 1 in 2 million. It is characterized by congenital foot deformities and multiple heterotopic ossifications in fibrous tissue. It usually starts with painful soft tissue swellings occurring with attacks at the ages of three or four. The attacks develop spontaneously or after minor trauma, and gradually turn into heterotopic ossifications that cause joint limitations, growth defects, skeletal deformities and chronic pain. The average life expectancy is forthy, and most of the patients are lost due to pulmonary complications. FOP is often misdiagnosed as fibromatosis, desmoid tumour or cancer, bunion, myositis, arthritis and rheumatic diseases. After clinical suspicion, confirmatory genetic analysis should be used for the diagnosis. The treatment of FOP is currently supportive. An effective, proven method has not yet been established. Herein, we present an 18-year-old female patient with FOP who underwent different treatment modalities in a 5-year period. This case-based review reveals all available treatment approaches with at least 6-month follow-up for FOP in the literature.

Keywords Fibrodysplasia ossificans progressiva · Heterotopic ossification · Treatment

Introduction

Fibrodysplasia ossificans progressiva (FOP), is a rare, severely disabling, autosomal dominant connective tissue disease characterized by abnormal ossifications that occur in fibrous tissue such as skeletal muscles, tendons and ligaments spontaneously, after minor trauma or injections. Patients with FOP grow up normal until the first painful soft tissue swelling appears. One after another painful swelling gradually turns into multiple heterotopic ossifications (HOs) that ultimately cause disability such as joint limitations, growth defects, skeletal deformities and chronic pain. Eighty percent of patients have congenital foot deformities. Ninety-five percent of them experience their first attack before the age of 15 [1]. The average life expectancy is 45 years, and most of them are lost due to pulmonary complications like pneumonia which result from thoracic insufficiency syndrome (TIS). Ankylosis of costovertebral joints, ossification of intercostal or paravertebral muscles, and spinal deformities lead to TIS that prevents normal chest wall expansion [2]. The primary aim of clinical care in FOP is to avoid trauma. Nevertheless, side effects of invasive diagnostic or therapeutic interventions are common because of diagnostic delay. FOP is often misdiagnosed as fibromatosis, desmoid

✉ Gulseren Akyuz
gulserena@gmail.com

Kardelen Gencer-Atalay
kardelengencer@gmail.com

Ekim Can Ozturk
ekimtrilogy@gmail.com

Ilker Yagci
drilkery@yahoo.com

Pinar Ata
pinaren@gmail.com

Kenan Delil
delilkenan@gmail.com

Zerrin Ozgen
zerrinozgen@gmail.com

1 Department of Physical Medicine and Rehabilitation, Marmara University School of Medicine, 34899 Pendik Ust Kaynarca, Istanbul, Turkey

2 Department of Medical Genetics, Marmara University School of Medicine, Istanbul, Turkey

3 Department of Radiation Oncology, Marmara University School of Medicine, Istanbul, Turkey

tumour or cancer, bunion, myositis, arthritis and rheumatic diseases [3]. Other hereditary and acquired HOs should also be considered in differential diagnosis [4]. Correct diagnosis can be made with confirmatory genetic testing. Heterozygous activating mutations (mostly c.617G> A; R206H) in activin receptor 1A/ activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type 1 receptor, have been identified in all sporadic and familial cases of FOP [4, 5]. The treatment of FOP is currently supportive. An effective, proven method of prevention or treatment has not yet been established. Short-term usage of high-dose corticosteroids seems to be prominent for reducing flare-up symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, leukotriene inhibitors and mast cell stabilizers might be useful in flare-ups and chronic stage. Aminobisphosphonates may have beneficial effects in decreasing the number of flare-ups, but the mechanism is still unclear [6]. Small doses of fractionated radiotherapy might have positive results in the early stage of HO [7]. Rehabilitation methods to improve pulmonary function, to enhance muscle strengthening and joint mobilization seem to be helpful for activities of daily living [5]. Surgical excision is not recommended in these patients. If surgery is inevitable, corticosteroids should be considered to inhibit ossification in the wound area [8]. Herein, we present an 18-year-old female patient with FOP who underwent different treatment modalities in a 5-year period. This case-based review reveals all available treatment approaches with at least 6-month follow-up for FOP in the literature.

Case report

An 18-year-old female patient was admitted to our outpatient clinic in December 2013. She had limitations in multiple joints and was currently suffering from pain in her left knee. She had C-typed mild thoracolumbar scoliosis on the left side and needed an assistant to walk with her head down, trunk and knees flexed. She had bilateral congenital great toe deformity (Fig. 1). The first soft tissue swelling was noticed in her submental area at the age of seven. It was painful until healed with stiffness. After this lesion, she had multiple similar attacks in other joints which led to limit movements. She didn't have any other findings in her medical history, and there was no sign of any genetic disorder in her family history. In physical examination range of motions (ROMs) of the neck, bilateral shoulder, elbow and hip joints were found to be decreased. Left knee flexion was painful and limited to 80° by goniometric measurement. Chest expansion was 2.5 cm. Visual analog scale (VAS) was questioned for global pain assessment and was found 8/10. In the ultrasonographic examination of the left thigh, adductor muscles and subcutaneous tissue were found to be edematous. Multiple HOs were seen in both plain radiographs

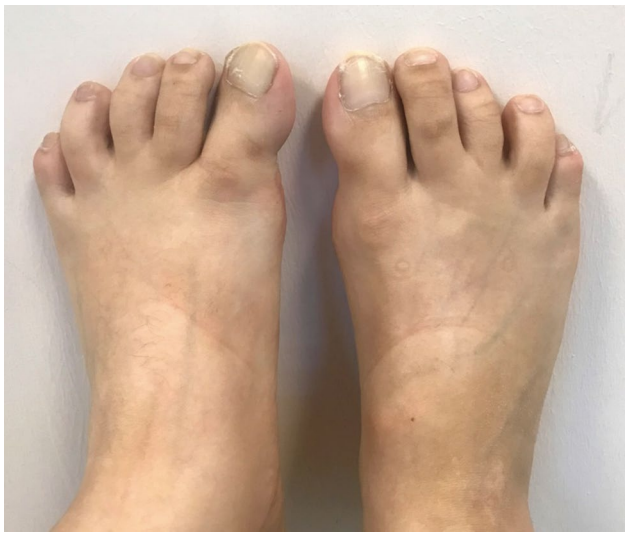

Fig. 1 Bilateral congenital great toe deformity of the patient

and whole body three-phase bone scintigraphy. In the laboratory examination, calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone, CRP, ESR, liver and kidney function tests were found to be within normal levels. Chromosome analysis revealed 46,XX. FOP was suspected, and the patient was consulted to the Department of Medical Genetics. In accordance with this, ACVR1 (102576) gene c.617G > A (p.Arg206His) mutation was detected at Sanger DNA sequencing analysis. In the treatment, oral prednisolone 48 mg/day and indomethacin 150 mg/day were started. Strengthening, ROM and diaphragmatic breathing exercises were begun. Passive stretching against to limitation of knee flexion was added additionally. At the end of the first week, VAS value was decreased to 5, and left knee flexion increased to 90°, while the patient was able to walk independently. Prednisolone was gradually tailored to 4 mg/day within 4 weeks. On the first-month control, VAS value decreased to 3, and knee flexion movement increased to 100 degrees. Oral corticosteroid treatment was ceased. However, pain and stiffness of the left knee recurred 4 months later (Figs. 2b, 3b). Attack was regressed after 16 mg/day of prednisolone was started over. Oral risedronate sodium 35 mg weekly and vitamin D 1200 IU/day were also added. In the first year examination, remission remained. The adequate dose of prednisolone was adjusted depending on the occurrence of symptoms. However, it could never be lowered below than 4 mg/day. On the third-year control, the patient was still able to walk by her own, there was not any surge in VAS score, any sign of new swelling or more restriction in ROMs. Unfortunately, cushingoid appearance could be seen. A few months later she showed up with complain of tenderness and pain in her left knee again. Swelling of the medial and posterior region of the knee was observed, and ROM was restricted. She was hardly able to walk. New bone formations extending

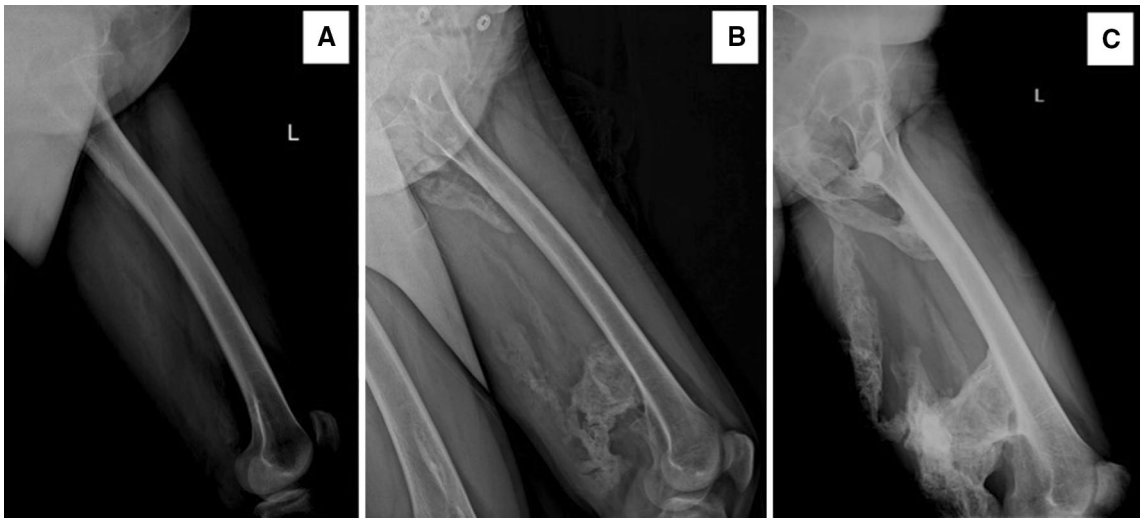

Fig. 2 Lateral plain radiographic images of the left femur **a** January 2014, **b** May 2014, **c** January 2018

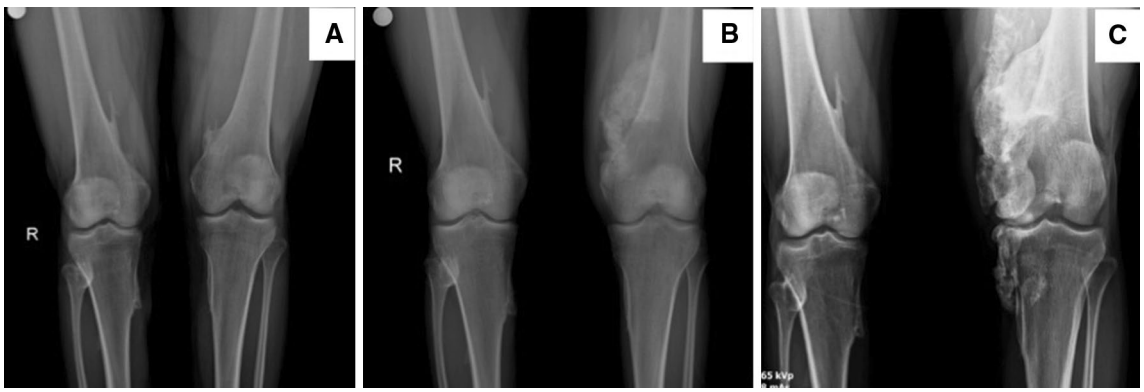

Fig. 3 Anteroposterior plain radiographic images of the knees **a** January 2014, **b** May 2014, **c** January 2018

to the medial and posterior side of the femur were detected in the plain radiographs (Figs. 2c, 3c). Since pain relief and improvement in ROM could not be managed with corticosteroid and bisphosphonate therapy, the patient was consulted to the Department of Radiation Oncology. She was given a dose of 2000 cGy in 10 fractions of radiotherapy for 2 weeks. At the end of ten sessions, pain relief was procured, ROM was increased, and the ambulation improved. But, there was no significant radiographic change between Hounsfield unit measurements of bone formation in computed tomography before and after radiotherapy [9]. The patient was discharged with a prescription of prednisolone 4 mg/day, vitamin D 1200 IU/day and risedronate sodium 35 mg weekly. She was advised to continue her medicine and exercise program. 6 months later, a new HO developed in her right buttocks. Her trunk was tilted to the right side; right hip ROMs were painful and limited. She was not able to walk or dress-up without help. Serum ALP level was found to be elevated in the laboratory examination. HO was thought to be in initial stage. Prednisolone was increased to 48 mg/day, and bisphosphonate treatment was switched to intravenous zoledronic acid 5 mg/year. Since there was no sign of improvement in 2 weeks, another dose of 2000 cGy radiotherapy was applied inside the right gluteal muscles. Significant improvement in the hip and trunk mobility was achieved after 10 session of radiotheraphy. The patient was able walk and dress-up independently without pain. Shoelift was adjusted to the left sole to facilitate walking difficulty due to leg length discrepancy associated with left knee flexion contracture. The patient was discharged with prednisolon 4 mg/d and home-based exercise program.

Discussion

Pubmed/MEDLINE, Scopus and Web of Science for English-language sources were searched using the terms ‘Fibrodysplasia Ossificans Progressiva’ and ‘treatment’, ‘corticosteroid’, ‘rehabilitation’, ‘bisphosphonates’, ‘surgical

treatment' or 'radiotherapy'. Case reports and clinical trials that published in the last 10 years (between January 2009 and June 2018) were included. Articles with at least 6 months follow-up period after treatment were eligible. Case reports about dental or malignancy that related with FOP were excluded. The literature search resulted in 95 non-duplicated records; 47 of which were excluded, because they were irrelevant including subjects with myositis ossificans and other chronic conditions, and 34 of which were eliminated, because of dental problems, no treatment and the short period of follow-up after treatment. Remaining 14 articles (8 with non-interventional treatment; 6 with interventional treatment) were included. The flow chart for the elimination of the articles is shown in Fig. 4.

Non-interventional treatment

Seven case reports and one clinical trial for non-invasive treatment were found in the literature (Table 1). Rogoveanue et al. reported a 36-year old female patient with FOP who was followed for 13 years. NSAIDs, cyclo-oxygenase inhibitors and physical therapy modalities including electrotherapy, massage, cryotherapy and biofeedback were used to reduce pain. Tolperasin chlorate, gabapentin, passive muscle stretching and PNF-hold-relax techniques were applied to increase joint mobility. Diaphragmatic breathing and inspiratory resistance exercises were performed to improve respiratory function. During the follow-up period pain reduced, nutritional and mental status improved, however, joint limitations and motor skills remained similar [10]. Bouvard et al. reported a patient who was diagnosed with FOP at the age of 5, was started medical treatment at 12. The patient fractured his right humerus at the age of 29. A retaining device was preferred to stabilise the bone. NSAIDs and high dose glucocorticoids were given during flare-up periods, while various bisphosphonates were used continuously [11]. Ulusoy reported a 29-year-old patient who referred to rheumatology clinic with a preliminary diagnosis of polymyositis. He had recurrent painful soft tissue swellings which turned into ossifications. FOP was clinically suspected, and oral etidronate therapy was begun to prevent new ossifications. But there was no confirmation with genetic analysis. General condition and ambulation did not deteriorate during the 1 year of follow-up [12]. Gatti et al.

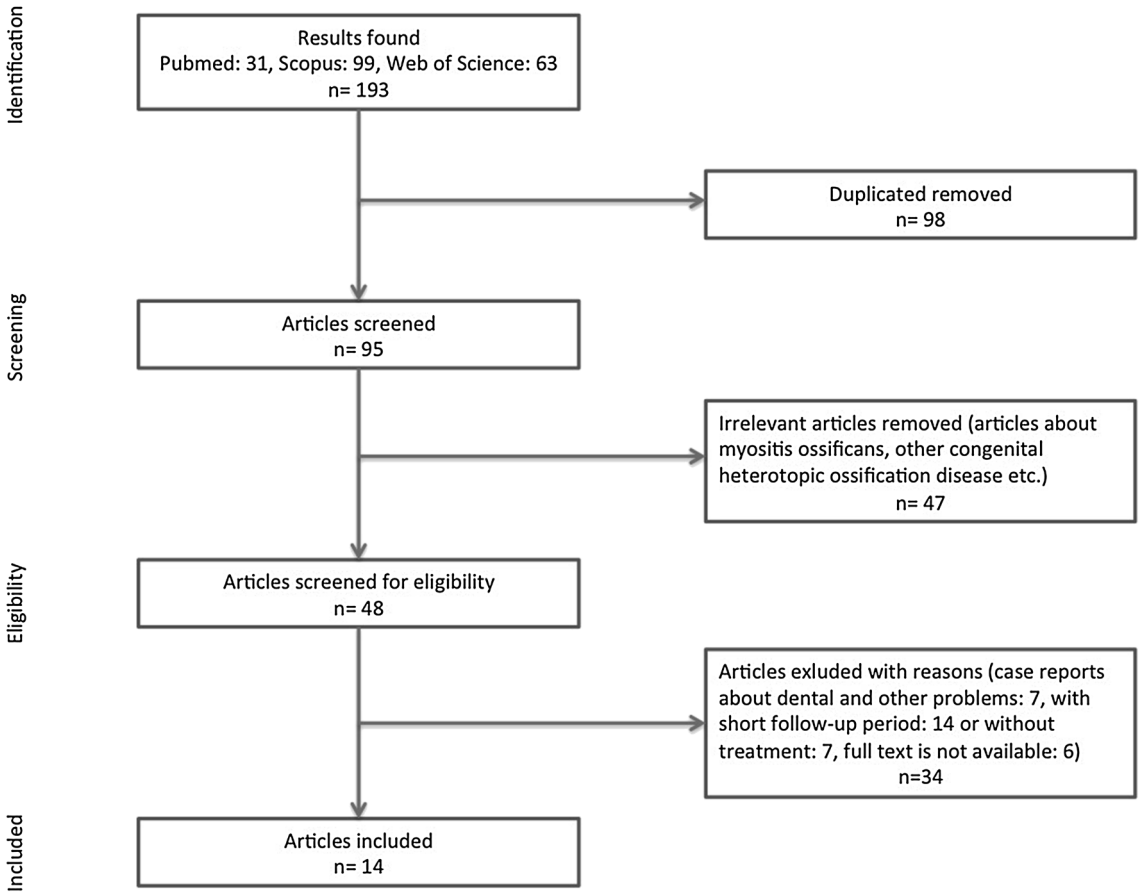

Fig. 4 Elimination process of the articles selected to the review

Table 1 Included articles that report non-interventional treatment of FOP

Article	Patient characteristics	Concurrent medication or radiation use	Follow-up period
Rogoveanu et al.	A 36-year-old patient	Analgesics, gabapentin, pyhsical therapy agents, and respiratory exercises	13 years
Bouvard et al.	A 29-year old patient who was diagnosed with FOP at the age of 5	NSAIDs and corticosteroids during flare-up periods, continuously oral or intravenous bisphosphonates, and respiratory exercises	17 years (not clear)
Ulusoy	A 29-year-old patient who was diagnosed without genetic confirmation	Oral etidronate and home-based exercise program	1 year
Gatti et al.	A 48-year-old patient who had frequent flare-ups	Oral etidronate with high dose prednisone during flare-up periods, and rosiglitazone	7 years
Palhares et al.	Two pediatric cases, both diagnosed with FOP before the age of 3	Ascorbic acid and clodronate	Case-1: 4 years Case-2: 9 years
Kaplan et al.	Two cases of patients with FOP who were 3 and 9 years old	Rapamycin and high dose corticosteroids	Case-1: 3 months Case-2: 18 years
Kaplan et al.	Case series of seven children aged between 2 and 13 years	Corticosteroids, NSAIDs, cyclo-oxygenase inhibitors or bisphosphonates, and imatinib (in six of them)	3 to 12 months
Kitoh et al.	Five patients with FOP; average age 23.4 years	Perhexiline maleate	2 years

reported a 48-year-old patient who had frequent flare-ups. The acute phase of each episode was lasted a few weeks and was ended-up with new calcifications. Corticosteroid and bisphosphonate treatments did not provide any clinical benefit, thus the authors started rosiglitazone therapy. After 1 and a half years of rosiglitazone treatment, there was no new flare-up, on the contrary, significant clinical improvements were detected [13]. Palhares et al. reported two pediatric cases, both diagnosed with FOP before the age of 3. Patients received intravenous clodronate during flare-up periods while oral ascorbic acid was used continuously. Frequency and severity of flare-ups were reduced during the treatment [14]. Kaplan et al. reported two patients with FOP who received rapamycin. The first case was a 3-year-old girl who did not respond to intravenous corticosteroids, montelukast, and NSAIDs. She was treated with rapamycin for 3 months; however, new attacks continued to occur. The second case had to receive rapamycin therapy for immunosuppression as he had liver transplantation due to cytomegalovirus infection. Rapamycin did not affect disease progression in both cases, even though it had been shown to be successful in animal models [15]. In a case series reported by Kaplan et al. seven patients with FOP were found to be unresponsive to corticosteroids, NSAIDs, cyclooxygenase inhibitors or bisphosphonates. Intensity and frequency of flare-ups were decreased after receiving imatinib therapy. This report highlighted that imatinib might also affect the signaling pathways implicated in the pathogenesis of HO, although its actual effect is to target BCL-ABL fusion protein in chronic myeloid leukaemia [16]. Kitoh et al. published the only clinical trial that included in this case-based review was designed to investigate the efficacy and safety of perhexiline maleate in the treatment of FOP. Five patients were treated with perhexiline maleate for 12 months and followed for 2 years. The authors suggested that perhexiline maleate within the safety doses was not significantly effective in FOP because new HOs developed in two patients [17].

Interventional treatment

Six cases with interventional treatments were reported in the literature (Table 2). Ozkan et al. reported a 21-year-old female who was presented with left chest pain and dyspnea. A heterogeneous mass in upper-medium part of left hemithorax was detected on computed tomography. FOP diagnosis was made with the histopathologic examination after surgical excision of the lesion. No recurrence was observed during the 1-year follow-up period [18]. Seok et al. reported another case with a painful mass on the chest wall. The patient was a 10-year-old boy who complained about the progressive limitation of his right shoulder movements. Oral naproxen and active ROM exercises started after the excision of HO between the pectoralis major and minor muscles. Full ROM was achieved by the fifth day after the operation and remained the same during 9-month follow-up [19]. Jayasundara et al. reported a 47-year old male who presented with progressive restriction of both shoulders and hips in 1 year period. He underwent four surgical resections, one joint at a time, within 2 years. Although remarkably improvements gained in all four joints, both hips became more limited approximately 9 months after surgeries. Bisphosphonate was started after this failure but could not also prevent progression. Another HO in the right thigh which created pressure necrosis of soft tissue and skin, appeared 6 years after the first admission. The fifth surgery was applied

Table 2 Included articles that report interventional treatment of FOP

Article	Patient characteristics	Intervention concurrent medication or radiation use	Follow-up period
Ozkan et al.	A 21-year-old patient who presented with left chest pain and shortness of breath	Surgical excision of partial rib and heterotopic bone structure with left thoracotomy approach Not mentioned	1 year
Seok et al.	A 10-year old patient who had heterotopic ossification on the anterior chest wall	Surgical excision of heterotopic ossification from the right chest Postoperative oral naproxen and active physiotherapy	9 months
Jayasundara et al.	A 47-year old patient who presented with progressive restriction of both shoulder and pelvic girdles in a period of one year	Four surgical excisions of ossific mass around both shoulders and hips, within 2 years. Another surgical resection 4 years later Indomethacin after the first four operations and radiotherapy after the last. Intravenous and oral bisphosphonates between fourth and fifth surgery	6 years
Duan et al.	A 17-year old patient who had ankylosis of the right hip and temporomandibular joints	Surgical excisions of heterotopic ossifications from right hip and both temporomandibular joints at the same session Postoperative oral indomethacin and etidronate, and functional exercises	2 years
Moore et al.	Three cases of patients with FOP who developed severe chin-on-chest deformity	Case-1 and Case-3 had operative correction of deformity Case-3 used NSAIDs until surgery	Case-1: 5 years Case-3: 20 years
Grobelny et al.	A 34-year old patient who was diagnosed with FOP at the age of 26, presented with myelopathy due to a heterotopic bone formation	Thoracic laminectomy for decompression of spinal cord Intravenous dexamethasone prior to surgery and oral prednisone after surgery	1 year

to remove this lesion and followed by radiotherapy [20]. Duan et al. reported a 17-year old boy who had ankylosis of the right hip and both temporomandibular joints. HOs were removed from these joints at the same session. NSAIDs and oral etidronate were given after surgery. Adequate eating and walking abilities were maintained during 2 years of follow-up [21]. Moore et al. reported three cases of FOP patients who had severe chin-on-chest deformities due to HOs around the neck. Two of them were operated successfully, while one was followed without surgery because of the high risk of complications. Satisfied long-term results were noted in both patients who underwent deformity correction [22]. Grobelny et al. reported a 34-year old patient with FOP who had progressive weakness of lower extremities and gait difficulty. A local heterotopic bone formation that caused spinal cord compression was detected at T9-10 level by radiologic evaluation. Thoracic laminectomy and short-term corticosteroid therapy provided significant improvements in muscle strength and gait ability. Although a new subcutaneous ossific mass was found, there was still no sign of compression in the thoracic spine 12 months after surgery [8].

This case-based review was aimed to reveal all available treatment approaches with at least 6-month follow-up for FOP in the literature. Short-term usage of corticosteroids and NSAIDs for acute flare-up periods and bisphosphonates for the chronic stage were found to be more preferred in most of the studies. Similarly, in this case, these agents were opted to use; however, corticosteroid usage was continued long-term due to progression in joint limitation and pain after cessation. Although this had led to the cushingoid appearance in the patient, a small dose of corticosteroid was decided to proceed with bisphosphonate treatment. Besides, radiotherapy was applied to the HOs which prevented the ambulation level of the patient. Significant improvements were observed in walking ability after radiotherapy sessions. Consistently, a few cases have been reported that radiotherapy may be effective in patients with FOP [23, 24]. Long-term follow-up studies which investigate the effectiveness of radiation in this disease are needed. In general, invasive intervention is not recommended in FOP patients, but this case-based review revealed some successful surgical interventions. These results suggest that the surgery decision can be made in selected cases after the analysis of benefit and loss. In the last 10 years since the discovery of the determinant gene, research in the underlying pathology of FOP has progressed impressively. So far an effective treatment is not available to cure FOP, however, on a molecular basis and mice models some agents were found to be promising good results [25, 26]. Among these agents, perhexiline maleate, rapamycin, and imatinib were used in FOP patients. Imatinib was found to have positive effects while the others appeared to be not significantly effective. Dorsomorphin, Activin-A antibody, palovarotene,

dipyridamole, microRNAs and mast cell inhibitors are still being searched for the inhibition of heterotopic ossification in different ways [25, 26].

Conclusion

Current findings about the pathophysiology of FOP are still insufficient and many targeted non-interventional and interventional techniques have been reported in the literature, but no consensus in the treatment has been provided yet. Nowadays, the importance of pharmacotherapy still preserved, rehabilitation methods and radiotheraphy are also emerging modalities in the treatment of FOP. Even some anecdotal reports address for effective treatment methods, the response to treatment seems to vary between patients. It has been suggested that the long term management of FOP and effectiveness of different therapy regimens can cause the structural changes in fibrous tissue although the reason of abnormal ossifications is unclear. The novel treatment approaches are giving hope for the future of FOP management. Further randomized controlled well-designed studies are needed in the treatment of FOP, and personalized management strategies also required in clinical practice.

Author contributions All co-authors have met all four criteria for authorship according to the International Committee of Medical Journal Editors (ICMJE).

Compliance with ethical standards

Conflict of interest KGA declares that she has no conflict of interest. ECO declares that he has no conflict of interest. IY declares that he has no conflict of interest. PA declares that she has no conflict of interest. KD declares that he has no conflict of interest. ZO declares that she has no conflict of interest. GA declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in the study.

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