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REVIEW ARTICLE

A Comprehensive Review on Stone Man Syndrome

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Abstract: Stone Man Syndrome also called as Fibrodysplasia ossificans progressiva (FOP) represents one of the most severe disorders of heterotopic ossification in humans, characterized by progressive transformation of soft tissues into bone. This rare genetic condition, affecting approximately 1 in 2 million individuals globally, results from mutations in the ACVR1 gene, which encodes the bone morphogenetic protein (BMP) type I receptor. The hallmark features include malformation of the great toes present at birth and progressive heterotopic ossification that typically begins in childhood. The heterotopic ossification follows a characteristic anatomic pattern, starting in the dorsal, axial, cranial, and proximal regions of the body, subsequently proceeding in a peripheral, ventral, and distal direction. Flare-ups often occur spontaneously or following trauma, leading to inflammation and subsequent bone formation. Early diagnosis remains crucial yet challenging, with many patients initially misdiagnosed with other conditions. Recent advances in understanding the molecular pathways involved in FOP have led to promising therapeutic strategies, including the development of ACVR1 inhibitors and the recent FDA approval of Palovarotene (SOHONOS). Management primarily focuses on preventing complications and maintaining quality of life through multidisciplinary care. Despite these advances, significant challenges remain in developing effective treatments that can halt or reverse disease progression. This paper explores the current knowledge of FOP's pathogenesis, clinical manifestations, diagnostic approaches, and therapeutic strategies, emphasizing the importance of early recognition and appropriate management to optimize patient outcomes.

Keywords: ACVR1 mutation; Heterotopic ossification; Genetic disorders, Bone morphogenetic protein; Progressive disability; Stone Man Syndrome.

1. Introduction

Fibrodysplasia ossificans progressiva (FOP), historically known as Münchmeyer's disease or stone man syndrome, stands as one of the most debilitating forms of heterotopic ossification known in medicine [1]. First documented in 1692 by Guy Patin, this condition transforms soft connective tissues into bone through a process of progressive heterotopic ossification [2]. The disorder manifests with remarkable precision and predictability, following a characteristic anatomical pattern that significantly impacts patient mobility and quality of life [3].

The genetic basis of FOP lies in mutations of the ACVR1 gene, which encodes the activin A receptor type I, a crucial component of the bone morphogenetic protein (BMP) signaling pathway [4]. The most common mutation, R206H, results in constitutive activation of the receptor, leading to dysregulated bone formation [5]. This genetic anomaly creates a complex cascade of cellular events that ultimately results in the formation of mature heterotopic bone through an endochondral process [6].

Clinical recognition of FOP typically begins with the observation of congenital malformations of the great toes, a characteristic feature present at birth [7]. The progression of heterotopic ossification usually initiates during the first decade of life, often triggered by trauma or inflammation [8]. This progressive ossification follows a distinct pattern, initially affecting the dorsal (Figure 1), axial, and proximal regions before advancing to ventral, appendicular, and distal areas [9].

Despite its rarity, affecting approximately one in two million individuals worldwide, FOP's impact on affected individuals is profound and life-altering [10]. The condition presents unique challenges in diagnosis and management, as traditional interventions such as surgical removal of heterotopic bone or muscle biopsies can exacerbate the condition [11-14].

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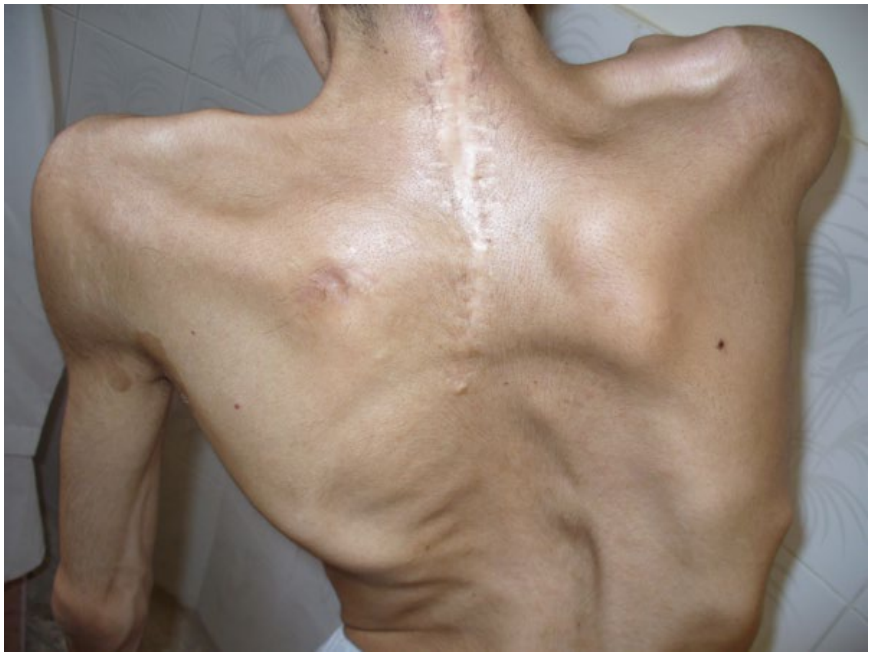

Figure 1. Body deformity and incision lines on the back of the patient in Stone Man Syndrome (Image Source: Mortazavi H, I J Radiology)

2. Epidemiology

Fibrodysplasia ossificans progressiva represents one of the rarest known genetic conditions, with a global prevalence of approximately one case per two million individuals [14]. The condition shows no preference for gender, race, or ethnic background, affecting males and females equally across all geographical regions [15]. Worldwide documentation indicates approximately 800 confirmed cases, though this figure likely underestimates the true prevalence due to misdiagnosis and limited access to genetic testing in many regions [16].

The age of clinical presentation typically occurs within the first decade of life, with the majority of cases diagnosed between ages 2 and 5 years [17]. However, the congenital hallmark of malformed great toes is present at birth, offering an opportunity for earlier recognition if properly identified [18]. The life expectancy of individuals with FOP is significantly reduced, with median survival estimated at 40 years, primarily due to cardiorespiratory complications resulting from restricted chest wall movement [19].

2.1. Genetic Basis and Molecular Mechanisms

The molecular foundation of FOP centers on mutations in the ACVR1 gene, located on chromosome 2q23-24 [20]. The canonical mutation, p.R206H, accounts for approximately 97% of cases, while several variant mutations have been identified in the remaining 3% [21]. This mutation results in constitutive activation of the BMP signaling pathway (Figure 2), leading to dysregulated bone formation.

The pathogenic mechanism involves complex cellular interactions:

2.1.1. Enhanced BMP Signaling:

The mutated ACVR1 receptor exhibits heightened sensitivity to BMPs and, uniquely, responds to activin A as a BMP-like agonist rather than an antagonist [22]. This altered signaling creates a pro-osteogenic environment in tissues that normally should not undergo ossification.

2.1.2. Cellular Transformation:

The process involves transformation of various cell types, including endothelial cells and muscle-resident fibro-adipogenic progenitors, into osteogenic precursors [23]. This cellular plasticity contributes to the progressive nature of the condition.

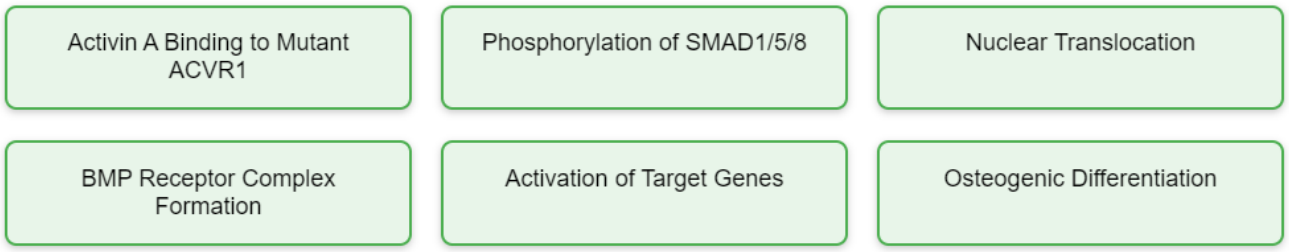

Figure 2. Molecular Signalling in FOP

2.1.3. Inflammatory Response:

The disease progression is marked by episodic flare-ups characterized by inflammation, which triggers the transformation of soft tissues into heterotopic bone through endochondral ossification [24-25]. These episodes often occur spontaneously or following minimal trauma, indicating the hair-trigger nature of the inflammatory response in FOP

3. Clinical Manifestations

3.1. Early Presentation

The clinical course of FOP typically manifests through two distinct hallmarks. The first presents at birth with characteristic malformations of the great toes, including hallux valgus, shortened first metatarsals, and monophalangism [26]. These malformations serve as crucial diagnostic indicators, though they are frequently overlooked or misinterpreted during initial medical evaluations [27].

Table 1. Clinical Features and Progression Patterns in FOP

Age Stage	Primary Manifestations	Clinical Characteristics	Common Complications
Birth - 2 years	Initial Presentation	Malformed great toes, Normal development	Rarely, lymphedema
2-10 years	Early Disease	First flare-ups, Neck and upper back involvement	Limited neck mobility
10-20 years	Progressive Stage	Shoulder and hip involvement, Progressive immobility	Restricted joint movement
20-30 years	Advanced Stage	Thoracic involvement, Widespread heterotopic bone	Respiratory compromise
>30 years	Late Stage	Complete joint ankylosis, Thoracic restriction	Cardiopulmonary complications

3.2. Progressive Ossification

The second hallmark emerges during early childhood, characterized by episodes of progressive heterotopic ossification. This process follows a predictable anatomical pattern, initially affecting the dorsal paraspinal muscles and progressing to the shoulder girdle, upper extremities, and eventually involving the hips and lower extremities [28]. The temporal progression typically begins in the first decade of life, with most patients experiencing their first flare-up by age five [29].

3.3. Flare-up Episodes

Flare-ups manifest as painful, warm, erythematous swellings that progress through stages of inflammation, fibroproliferation, and eventual ossification. These episodes may be triggered by minor trauma, viral infections, muscular stretching, or can occur spontaneously [30]. During these periods, patients often experience systemic symptoms including low-grade fever, malaise, and severe localized pain [31].

3.4. Musculoskeletal complications

The cumulative effect of progressive ossification leads to severe restriction of joint mobility and eventual ankylosis. The formation of bony bridges across joints results in characteristic postural abnormalities and severely limited range of motion [32]. The temporomandibular joint involvement frequently leads to restricted jaw movement, affecting speech and nutrition [33].

3.5. Respiratory Complications

As the disease progresses, involvement of the chest wall musculature and costovertebral joints significantly impacts respiratory function. Restrictive lung disease develops as the thoracic cavity becomes increasingly rigid, leading to reduced vital capacity and increased susceptibility to respiratory infections [34].

3.6. Effect on sense organs

Many patients experience progressive hearing impairment due to middle ear ossification. Additionally, the fusion of cervical vertebrae can affect balance and coordination [35]. These sensory complications add another layer of complexity to the already challenging clinical picture.

3.7. Quality of Life Impact

The progressive nature of FOP significantly impacts activities of daily living. Most patients require mobility assistance by their teenage years, with many becoming wheelchair-dependent by early adulthood [36]. The condition affects educational pursuits, career choices, and social interactions, necessitating comprehensive support systems and adaptive strategies.

4. Diagnosis

4.1. Clinical Assessment

Early recognition of FOP demands meticulous clinical evaluation. Primary diagnostic indicators include characteristic great toe malformations and the pattern of heterotopic ossification. Physical examination reveals progressive limitation of joint mobility and the presence of hard, irregular masses within soft tissues [37]. The sequential pattern of ossification, typically beginning in the neck and upper back regions, provides crucial diagnostic clues for clinicians [38].

Table 2. Diagnostic Criteria and Assessment Tools for FOP

Diagnostic Category	Major Criteria	Minor Criteria	Assessment Methods
Clinical Features	Malformed great toes	Progressive HO*	Physical examination
Radiological Signs	Cervical spine malformations	Scalp osteomas	X-rays, CT scans
Genetic Testing	ACVR1 R206H mutation	Variant mutations	DNA sequencing
Laboratory Findings	None specific	Elevated ALP** during flares	Blood tests
Functional Assessment	CAJIS*** score	FOP-PFQ****	Clinical evaluation

*HO: Heterotopic Ossification; **ALP: Alkaline Phosphatase; ***CAJIS: Cumulative Analogue Joint Involvement Scale;
****FOP-PFQ: FOP Physical Function Questionnaire

4.2. Radiological findings

Radiographic imaging serves as a cornerstone in FOP diagnosis and monitoring. Plain radiographs demonstrate the classic malformation of great toes and reveal sheets and plates of heterotopic bone formation in characteristic anatomical locations [39]. Computed tomography (CT) scans provide detailed three-dimensional visualization of heterotopic ossification patterns and help assess the extent of joint involvement [40].

4.3. Molecular Genetic Testing

Definitive diagnosis relies on genetic analysis identifying mutations in the ACVR1 gene. The most common R206H mutation can be detected through targeted DNA sequencing [41]. Genetic testing holds particular importance in cases with atypical presentations or when diagnostic uncertainty exists. Early genetic confirmation helps avoid unnecessary invasive procedures that could exacerbate the condition [42].

4.4. Laboratory Findings

While not diagnostic, certain laboratory parameters may support clinical suspicion. During flare-ups, elevated inflammatory markers including erythrocyte sedimentation rate and C-reactive protein may be observed. Alkaline phosphatase levels, particularly bone-specific isoforms, often increase during active bone formation phases [43].

4.5. Differential Diagnosis

Several conditions require careful differentiation from FOP. These include:

Progressive osseous heteroplasia shows similar heterotopic ossification but follows a different pattern and lacks toe malformations. Soft tissue tumors, particularly aggressive juvenile fibromatosis, may initially present similarly but demonstrate distinct radiological features. Post-traumatic ossification presents with localized bone formation and clear trauma history [44].

4.6. Diagnostic Challenges

Misdiagnosis remains common, often leading to harmful interventions. Diagnostic delays frequently occur due to the rarity of FOP and variable early presentations. Awareness of characteristic clinical features and appropriate diagnostic algorithms is crucial for early recognition [45].

4.7. Biomarkers

Recent research focuses on identifying reliable biomarkers for disease activity and progression. Elevated levels of cartilage-derived proteins and specific inflammatory mediators show promise as potential markers for monitoring disease activity and therapeutic response [46].

4.8. Prenatal Diagnosis

In families with known FOP mutations, prenatal genetic testing enables early detection. However, ethical considerations and counseling remain crucial components of prenatal diagnostic approaches [47].

5. Treatment and Management

5.1. Prevention

Management of FOP centers primarily on prevention of flare-ups and complications. Avoiding physical trauma, including intramuscular injections, dental procedures without proper precautions, and excessive muscle stretching, forms the cornerstone of preventive care [48]. Environmental modifications and protective measures help reduce fall risks and potential tissue injury [49].

Table 3. Current Treatment Approaches in FOP Management

Treatment Category	Interventions	Timing	Contraindications
Preventive Care	Activity modification, Fall prevention	Continuous	Contact sports, High-impact activities
Acute Flare Management	Glucocorticoids (Prednisone 2mg/kg/day)	Within 24h of flare	None if properly indicated
Chronic Management	Palovarotene (FDA approved)	As prescribed	Age <14 years
Supportive Care	Occupational therapy, Respiratory support	As needed	Forceful manipulation
Emergency Care	Customized protocols, Careful airway management	During emergencies	Intramuscular injections

5.2. Pharmacotherapy

5.2.1. Acute Flare Management

During acute flare-ups, glucocorticoids serve as first-line therapy, typically administered as a short course of high-dose prednisone within 24 hours of flare onset [50]. These medications help reduce inflammation and potentially limit the extent of heterotopic ossification. Non-steroidal anti-inflammatory drugs may provide additional benefit for pain management during less severe episodes [51].

Disease-Modifying Therapies: Recent advances have led to the development of targeted therapeutic approaches. Palovarotene (SOHONOS), a retinoic acid receptor γ agonist, received FDA approval for reducing heterotopic ossification in patients aged 14 and older [52]. This breakthrough represents the first approved treatment specifically targeting the underlying pathophysiology of FOP [53].

5.2.2. Clinical trials

Clinical trials investigating various therapeutic strategies include:

- Anti-inflammatory agents targeting specific pathways involved in heterotopic ossification
- ACVR1 inhibitors designed to modulate aberrant signaling
- Cell-based therapies aimed at preventing bone formation [54, 55].

5.3. Supportive Care

5.3.1. Respiratory Management

Regular pulmonary function monitoring and early intervention for respiratory complications remain essential. Chest physiotherapy and careful respiratory support during illness help maintain optimal lung function [56].

5.3.2. Nutritional Support

Dietary management becomes increasingly important as jaw mobility decreases. Consultation with nutrition specialists helps ensure adequate caloric and nutrient intake while minimizing choking risks [57].

5.3.3. Physical Medicine

Careful activity modification and adaptive equipment help maintain function and independence. Occupational therapy focuses on developing strategies for activities of daily living while avoiding triggers for flare-ups [58].

5.3.4. Pain Management

A multimodal approach to pain control incorporates both pharmacological and non-pharmacological strategies. Regular assessment and adjustment of pain management protocols help maintain quality of life [59].

5.4. Multidisciplinary Care

5.4.1. Coordinated Care Approach

Effective management requires coordination among various specialists including rheumatologists, orthopedists, pulmonologists, and physical medicine experts. Regular monitoring and communication between healthcare providers ensures comprehensive care delivery [60].

5.4.2. Psychological Support

The progressive nature of FOP creates significant psychological challenges. Professional counseling and support groups provide essential emotional support for patients and families [61].

5.4.3. Emergency Management

Development of individualized emergency protocols ensures appropriate care during acute medical situations. Education of emergency healthcare providers about FOP-specific concerns helps prevent iatrogenic harm [62].

6. Prognosis

6.1. Life Expectancy

The natural history of FOP significantly impacts life expectancy, with median survival approximately 40 years of age. Cardiopulmonary complications, primarily resulting from restrictive chest wall disease, represent the most common cause of mortality [63]. The progression rate varies among individuals, though certain patterns remain consistent across the patient population [64].

6.2. Functional Impact

Progressive loss of mobility typically occurs in a predictable sequence. Most patients require wheelchair assistance by their twenties, with complete loss of upper extremity function often following in subsequent decades. Despite these challenges, many individuals maintain cognitive function and can pursue educational and professional goals with appropriate adaptations [65].

6.3. Quality of Life

The impact on quality of life varies with disease progression and individual circumstances. Early diagnosis and appropriate management strategies can help optimize outcomes. While physical limitations increase over time, many patients develop remarkable resilience and adaptive capabilities [66].

6.4. Prognostic Factors

Several factors influence individual prognosis, including age at first flare-up, frequency of episodes, and extent of thoracic involvement. Early onset of flare-ups and rapid progression during childhood often correlate with more severe long-term outcomes [67].

7. Conclusion

Fibrodysplasia ossificans progressiva represents one of medicine's most challenging genetic disorders, characterized by its progressive and debilitating nature. The identification of the underlying genetic mutation has revolutionized our understanding of the condition and opened new therapeutic possibilities. The management of FOP requires a balance treatment strategy involving preventing complications and maintaining quality of life. While current therapeutic options remain limited, recent advances in targeted treatments offer hope for affected individuals

References

[1] Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva. J Bone Miner Res. 2010;25(12):2527-39.

[2] Connor JM, Evans DA. Fibrodysplasia ossificans progressiva. The clinical features and natural history of 34 patients. J Bone Joint Surg Br. 1982;64(1):76-83.

[3] Kaplan FS, Le Merrer M, Glaser DL, et al. Fibrodysplasia ossificans progressiva. Best Pract Res Clin Rheumatol. 2008;22(1):191-205.

[4] Shore EM, Xu M, Feldman GJ, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006;38(5):525-7.

[5] Chaikuad A, Alfano I, Kerr G, et al. Structure of the bone morphogenetic protein receptor ALK2 and implications for fibrodysplasia ossificans progressiva. J Biol Chem. 2012;287(44):36990-8.

[6] Yu PB, Deng DY, Lai CS, et al. BMP type I receptor inhibition reduces heterotopic ossification. Nat Med. 2008;14(12):1363-9.

[7] Kaplan FS, Xu M, Seemann P, 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(3):379-90.

[8] Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: clinical and genetic aspects. Orphanet J Rare Dis. 2011;6:80.

[9] Kaplan FS, Zasloff MA, Kitterman JA, et al. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-91.

[10] Shore EM, Kaplan FS. Inherited human diseases of heterotopic bone formation. Nat Rev Rheumatol. 2010;6(9):518-27.

[11] Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. Pediatrics. 2005;116(5):e654-61.

[12] Hatsell SJ, Idone V, Wolken DM, et al. ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A. Sci Transl Med. 2015;7(303):303ra137.

[13] Wentworth KL, Masharani U, Hsiao EC. Therapeutic advances for blocking heterotopic ossification in fibrodysplasia ossificans progressiva. Br J Clin Pharmacol. 2019;85(6):1180-7

[14] Di Rocco M, Baujat G, Bertamino M, et al. International physician survey on management of FOP: a modified Delphi study. Orphanet J Rare Dis. 2017;12(1):110.

[15] Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP). Bone. 2017;101:123-8.

[16] Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva: a comprehensive global assessment. J Bone Miner Res. 2016;31(3):650-6.

[17] Kaplan FS, Pignolo RJ, Shore EM. The FOP metamorphosis: Time for a systems approach. Bone. 2018;109:3-6.

[18] Mantick N, Bachman E, Baujat G, et al. The FOP connection registry: Design of an international patient-sponsored registry for fibrodysplasia ossificans progressiva. Bone. 2018;109:285-90.

[19] Kaplan FS, Zasloff MA, Kitterman JA, et al. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-91.

[20] Hildebrand L, Rossbach B, Kühnen P, et al. Fibrodysplasia ossificans progressiva (FOP): Watch the great toes! Eur J Pediatr. 2018;177(5):683-8.

[21] Hwang JH, Lee CH, Lee DG, Cho JY. Fibrodysplasia ossificans progressiva: a case report and review of literature. J Korean Med Sci. 2009;24(3):542-5.

[22] Wang H, Shore EM, Pignolo RJ, Kaplan FS. Activin A amplifies dysregulated BMP signaling and induces chondro-osseous differentiation of primary connective tissue progenitor cells in patients with fibrodysplasia ossificans progressiva (FOP). Bone. 2018;109:218-24.

[23] Chakkalakal SA, Zhang D, Culbert AL, et al. An Acvr1 R206H knock-in mouse has fibrodysplasia ossificans progressiva. J Bone Miner Res. 2012;27(8):1746-56.

[24] Yu PB, Deng DY, Beppu H, et al. Bone morphogenetic protein (BMP) type II receptor is required for BMP-mediated growth arrest and differentiation in pulmonary artery smooth muscle cells. J Biol Chem. 2008;283(7):3877-88.

[25] Kan L, Kessler JA. Evaluation of the cellular origins of heterotopic ossification. Orthopedics. 2014;37(5):329-40.

[26] Kaplan FS, Shore EM. Perspective: progressive osseous heteroplasia. J Bone Miner Res. 2000;15(11):2084-94.

[27] Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. Pediatr Endocrinol Rev. 2013;10(Suppl 2):437-48.

[28] Cohen RB, Hahn GV, Tabas JA, et al. The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 1993;75(2):215-9.

[29] Kaplan FS, Glaser DL, Shore EM, et al. The phenotype of fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab. 2005;3(3-4):183-8.

[30] Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva: a comprehensive global assessment. J Bone Miner Res. 2016;31(3):650-6.

[31] Kaplan FS, Pignolo RJ, Al Mukaddam M, Shore EM. Hard targets for a soft disease: managing fibrodysplasia ossificans progressiva. Bone. 2018;109:281-4.

[32] Morales-Piga A, Bachiller-Corral J, Trujillo-Tiebas MJ, et al. Fibrodysplasia ossificans progressiva in Spain: epidemiological, clinical, and genetic aspects. Bone. 2012;51(4):748-55.

[33] Connor JM, Evans DA. Extra-articular ankylosis in fibrodysplasia ossificans progressiva. Br J Oral Maxillofac Surg. 1982;20(2):117-21.

[34] Kussmaul WG, Esmail AN, Sagar Y, et al. Pulmonary and cardiac function in advanced fibrodysplasia ossificans progressiva. Clin Orthop Relat Res. 1998;346:104-9.

[35] Levy CE, Lash AT, Janoff HB, Kaplan FS. Conductive hearing loss in individuals with fibrodysplasia ossificans progressiva. Am J Audiol. 1999;8(1):29-33.

[36] Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: clinical and genetic aspects. Orphanet J Rare Dis. 2011;6:80.

[37] Kaplan FS, Xu M, Glaser DL, et al. Early diagnosis of fibrodysplasia ossificans progressiva. Pediatrics. 2008;121(5):e1295-300.

[38] Shore EM, Kaplan FS. Role of altered signal transduction in heterotopic ossification and fibrodysplasia ossificans progressiva. Curr Osteoporos Rep. 2011;9(2):83-8

[39] Delai PLR, Kantanie S, Santili C, et al. Fibrodysplasia ossificans progressiva: a hereditary illness of multidisciplinary interest. Rev Bras Ortop. 2004;39(4):205-13.

[40] Mahboubi S, Glaser DL, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva. Pediatr Radiol. 2001;31(5):307-14.

[41] Kaplan FS, Xu M, Seemann P, 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(3):379-90.

[42] Diagnostic and Management Considerations in FOP. JBJS Rev. 2019;7(8):e3.

[43] Baujat G, Choquet R, Bouée S, et al. Prevalence of fibrodysplasia ossificans progressiva (FOP) in France: an estimate based on a record linkage of two national databases. Orphanet J Rare Dis. 2017;12(1):123.

[44] Kaplan FS, Shore EM. Perspective: progressive osseous heteroplasia. J Bone Miner Res. 2000;15(11):2084-94.

[45] Pignolo RJ, Durbin-Johnson BP, Rocke DM, Kaplan FS. Joint-specific risk of impaired function in fibrodysplasia ossificans progressiva (FOP). Bone. 2020;140:115549.

[46] Wang H, Lindborg C, Lounev V, et al. Cellular Hypoxia Promotes Heterotopic Ossification by Amplifying BMP Signaling. J Bone Miner Res. 2016;31(9):1652-65.

[47] Kaplan FS, Murray JE, Sylvester JE, et al. The ethical imperative to treat rare disorders: principles and guidelines for managing fibrodysplasia ossificans progressiva. Bone. 2018;109:282-4.

[48] Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis and management. Curr Osteoporos Rep. 2013;11(2):179-86.

[49] Kaplan FS, Al Mukaddam M, Baujat G, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Proc Intl Clin Council FOP. 2019;1:1-111.

[50] Kaplan FS, Pignolo RJ, Al Mukaddam M. Bone morphogenetic protein signaling inhibition for the treatment of fibrodysplasia ossificans progressiva. Curr Osteoporos Rep. 2016;14(5):169-75.

[51] Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis and management. Curr Osteoporos Rep. 2013;11(2):179-86.

[52] Wentworth KL, Masharani U, Hsiao EC. Therapeutic advances for blocking heterotopic ossification in fibrodysplasia ossificans progressiva. Br J Clin Pharmacol. 2019;85(6):1180-7.

[53] Kaplan FS, Al Mukaddam M, Shore EM. Therapeutic approaches to fibrodysplasia ossificans progressiva. Bone. 2018;109:247-55.

[54] Chakkalakal SA, Uchibe K, Convente MR, et al. Palovarotene inhibits heterotopic ossification and maintains limb mobility and growth in mice with the human ACVR1R206H fibrodysplasia ossificans progressiva (FOP) mutation. J Bone Miner Res. 2016;31(9):1666-75.

[55] Haviv R, Moshe V, De Benedetti F, et al. A novel therapeutic approach for fibrodysplasia ossificans progressiva using IL-1β receptor antagonist. J Bone Miner Res. 2019;34(9):1657-66.

[56] Kaplan FS, Al Mukaddam M, Pignolo RJ. Acute and chronic care considerations for patients with fibrodysplasia ossificans progressiva. Curr Osteoporos Rep. 2020;18(5):531-40.

[57] Connor JM, Evans DA. Genetic aspects of fibrodysplasia ossificans progressiva. J Med Genet. 1982;19(1):35-9.

[58] Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva: a comprehensive global assessment. J Bone Miner Res. 2016;31(3):650-6.

[59] Kaplan FS, Zasloff MA, Kitterman JA, et al. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-91.

[60] Hsiao EC, Di Rocco M, Cali A, et al. Special considerations for clinical trials in fibrodysplasia ossificans progressiva (FOP). Br J Clin Pharmacol. 2019;85(6):1199-207.

[61] Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: clinical and genetic aspects. Orphanet J Rare Dis. 2011;6:80.

[62] Kaplan FS, Al Mukaddam M, Pignolo RJ. Emergency care of patients with fibrodysplasia ossificans progressiva. Muscle Nerve. 2019;59(4):397-403.

[63] Kaplan FS, Zasloff MA, Kitterman JA, et al. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am. 2010;92(3):686-91.

[64] Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva: a comprehensive global assessment. J Bone Miner Res. 2016;31(3):650-6.

[65] Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP). Bone. 2017;101:123-8.

[66] Mantick N, Bachman E, Baujat G, et al. The FOP connection registry: Design of an international patient-sponsored registry for fibrodysplasia ossificans progressiva. Bone. 2018;109:285-90.

[67] Shore EM, Kaplan FS. Insights from a rare genetic disorder of extra-skeletal bone formation, fibrodysplasia ossificans progressiva (FOP). Bone. 2008;43(3):427-33.