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Case report

Radiation Therapy in Treatment of Fibrodysplasia Ossificans Progressiva: A Case Report and Review of the Literature

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A B S T R A C T

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare genetic disorder with diffuse extra-skeletal bone formation. The genetic mutation responsible for FOP has recently been discovered and is connected with excessive activation of bone morphogenetic protein receptor. This disease usually begins with typical ossification pattern in early childhood, causing increasing disability and making patients totally disabled by the age of 30. Ectopic ossification develops spontaneously and can be triggered by any trauma and even intramuscular injections. The symptoms of FOP are often misdiagnosed as cancer, causing unnecessary biopsies, which can precipitate further progressive heterotopic ossification. There is no effective treatment for this severe condition. Radiotherapy can be helpful in impeding ossification, although the strict evidence for that is lacking. There are only two reports in the literature referring to the use of radiotherapy in treatment of FOP. Herein, we present a 35-year-old patient successfully treated with small doses of fractionated radiotherapy in several courses. This case indicates that radiotherapy can be useful in treating patients with FOP.

Key words: *fibrodysplasia ossificans progressiva, heterotopic ossification, radiotherapy*

Introduction

Fibrodysplasia ossificans progressiva (FOP), also known as myositis ossificans progressiva, is an extremely rare disease of the connective tissue. It affects approximately one in two million individuals, assuming there are only 300 known patients worldwide. Main characteristics of FOP are congenital skeletal malformations of the great toes and progressive heterotopic ossification in specific anatomic patterns leading to early disability[1]. Although genetic transmission is autosomal dominant, most cases are sporadic and arise as a result of a spontaneous new mutation[2]. During childhood new bone is being formed within soft connective tissue, such as skeletal muscle, tendon, and ligaments, making skeletal elements fuse with normal skeletal bone. Before being ossified, soft tissue gets swelled and inflamed. Heterotopic bone formation is episodic, with ossification generally occurring in a predictable sequence, starting in the upper back and neck region. This disease is progressive leading to an early disability due to contractures and joint fusions. Natural progressive course of the disease can be precipitated by soft tissue injury or any minor trauma, such as intramuscular injections. Furthermore, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises and falls may promote heterotopic bone formation at the site of injury and immobility. Attempts of doing biopsy or surgically removing heterotopic bone may risk provoking sudden and painful new bone growth[3]. There is no known effective treatment for FOP. Radiotherapy treatment might have some therapeutic effect in FOP although there is no firm evidence for that and the literature referring to radiotherapeutic treatment of patients with FOP is extremely scarce.

Case report

A 35-year-old female patient was diagnosed with FOP at age of four, when her parents had noticed a red, pain-

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ful gristle on her back, turning into a bone in few days. Till the age of 8, she was able to walk erected, but afterwards the back bone progressively got crooked, so by the age of 10 she could not erect herself any more. The spine became immobile due to ossification of the paravertebral muscles. On several occasions in her teenage period, she was treated with etidronate and peroral corticosteroid therapy (metilprednisolone), with noticeable results, leaving her without formation of new ossification foci for two years.

At the age of 25, the disease progressed in her right upper arm and both knees. The masticatory muscles were also affected, causing disability to open the mouth and consequential eating difficulties. The anecdotal fact is that the patient noticed subjective improvement of painful ossification symptoms after the X-ray examination of right upper arm and both knees, which revealed the onset of heterotopic ossification of the soft tissue around the joints.

The decision was made to treat the patient with radiotherapy for the first time in the course of her disease, after an informed consent was obtained. She received 10 Gy delivered in 5 fractions on the right upper arm and 8 Gy, delivered in two fractions, on both knees. Checkups after the treatment revealed a good long-term outcome: in the region of her right upper arm there was no further ossification radiologically proven for the next four years, while the radiographs of both knees revealed no further ossification within the 10 years' follow-up.

On the grounds of such favourable radiation response in patient, the decision was made to treat the patient with radiotherapy in case of trauma or onset of signs of ossification in particular region. The treatment decisions regarding the patient were made in multidisciplinary setting.

Two years later, flare-ups appeared on extremities, causing ossification around joints of hands and legs with consequently increasing immobility. Based on clinical status and computerised tomography (CT) findings, which revealed active heterotopic ossification in the region of proximal part of her right upper arm and distal part of her right upper leg, the radiation therapy was indicated. The patient received 2 Gy, delivered in two fractions on previously not irradiated, remaining part of her right upper arm and the same dose on the distal part of her right upper leg. Radiotherapy was also applied on the right, anterior part of her neck with 6 Gy delivered in 6 fractions, based on clinical finding of developing an initial heterotopic ossification.

At the moment radiotherapy was applied, the patient reported immediate remission of symptoms.

Control CT checkups of irradiated regions, performed biannually through the following four years, revealed stationary findings of heterotopic ossification. Because of respiratory limiting ossification of the right thoracic wall, the patient received radiotherapy of 4 Gy, delivered in 4 fractions on the ossificating area of right thorax. Two months later the radiation was delivered on the right infraclavicular area, due to the onset of active disease in that region. The patient received 4 Gy delivered in 4 fractions. Chest X ray checkups had been performed regularly and the last that was done 3 years ago revealed no further progression of the disease in the region of the right thoracic wall, but the active ossification was clinically and radiologically confirmed on the left anterior part of the neck. The last radiotherapy treatment was performed at the age of 34, on the affected area of neck, with dose of 3 Gy delivered in 3 fractions, in order to prevent ossification around larynx and to keep the airway intact. The patient was discharged from radiotherapy treatment with an immediate subjective improvement of symptoms. At the follow-up visits that were made six months and one year after the treatment, the clinical and radiological examinations revealed no ossification found in treated region, also with no functional lesions.

Regarding the timing of symptoms' improvement, the patient reported a clinical amelioration already within the first three days after the commencing of radiotherapy, throughout all radiotherapy courses.

During the last radiotherapy course the patient was 34-year-old, and had developed multiple joint contractures. Chest X-ray revealed deformation of all bony structures with osseous intercostal bridging (Figure 1). Abdominal CT was performed due to the onset of heterotopic ossification in abdominal wall. Definitive skeletal deformation and extensive heterotopic ossification were clearly demonstrated, but the positive impact of radiotherapy on both knees and right shoulder has remained till nowadays (Figure 2).

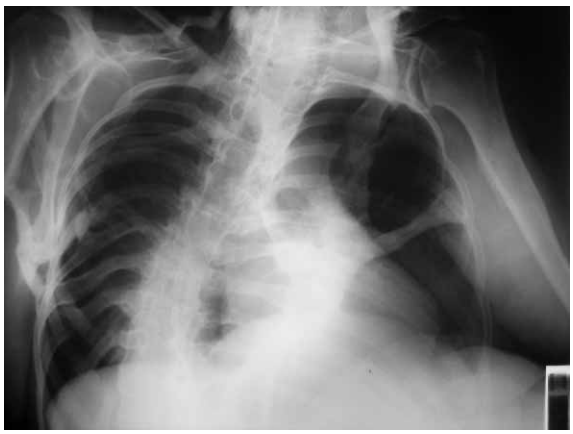

Fig. 1. Chest X-ray indicating thorax deformation, orthotopic ankylosis of the costovertebral joints, ossification of intercostal muscles and spine kyphoscoliosis.

Discussion

The misdiagnosis of FOP approaches 90 per cent of affected individuals worldwide. FOP is commonly misdiagnosed as aggressive juvenile fibromatosis, lymphedema, or soft tissue sarcoma. Seven patients, out of those misdiagnosed with cancer, received radiotherapy but

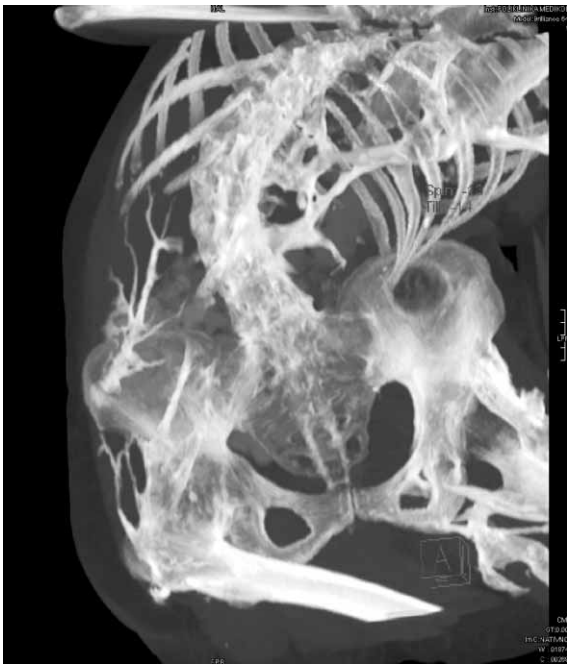

Fig. 2. Computed tomography maximum intensity projection (MIP) image demonstrating extensive irregular ossifications in lumbar subcutaneous fat, along right gluteal muscles from iliac crest to hip and in left thigh adductor muscles.

there has been no mention of the outcome[4]. Most patients with FOP are confined to a wheelchair by the third decade of life, and require lifelong assistance in performing activities of daily living. The median age of survival is approximately 41 years, and death often results from complications of thoracic insufficiency syndrome[5].

The genetic mutation leading to FOP has recently been discovered and linked to chromosome 2q23-24. The analysis revealed heterozygous mutation in the glycine--serin (GS) activation domain of ACVR1, a bone morphogenetic protein (BMP) type 1 receptor[6]. Additional mutations have been identified in the GS-domain and kinase domain of ACVR1 in individuals with atypical forms of FOP[7]. Protein homology modelling of the mutated receptor predicts destabilization of the glycine-serine (GS) activation domain, consistent with an overactive BMP signalling pathway as the underlying cause of the ectopic chondrogenesis, osteogenesis, and joint fusions seen in FOP[8].

Bone morphogenetic proteins (BMPs) constitute the group of growth factors involved in pivotal morphogenetic signalling, orchestrating tissue architecture throughout the body.

Moreover, BMPs have an important role in many physiological and pathophysiological processes, such as regeneration, repair, development of specific tissues and even a protective role against fibrotic processes in inflamation[9]. In addition with the fact that BMPs have ability to induce ectopic bone formation, the novel studies indicate that their expression in prostate cancers have been linked specifically with the tumour progression to bone and the development of osteosclerotic metastases[10].

Any kind of surgery in patients with FOP is harmful; it causes disease progression and should be avoided (except in emergencies). There are no established treatments for FOP and no clinical trials to assess the efficacy of any potential therapy. Since there is no effective treatment for FOP, it is of crucial importance to avoid any kind of soft tissue trauma, iatrogenic or accidental. Early diagnosis an avoidance of trauma are the basic principles of dealing with these patients.

Knowing the progressive nature of disease, we can assume further progression in the future. However, in our patient the radio- therapy, periodically undertaken during a relatively long period of ten years, helped with acute flare-ups and halted the disease progression. At first application of radiotherapy our patient was 25 year old and at last session of radiotherapy she was 34. It is ten year follow up from the first radiotherapy treatment. This patient received radiotherapy treatment on dominant sites of pathologic ossification (except on spine), with no side-effects. The leading positive effect of radiotherapy remained on the right shoulder and both knees with preserved limited range of motion.

It is well known that radiotherapy is effective and safely applied for post-traumatic forms of heterotopic ossification, following spinal injuries, postoperative formation of new bone and even for the prophylaxis of ossification at the time of bone surgery[11]. It can be deduced that there is a clinical and scientific background regarding use of radiotherapy in conditions of heterotopic ossification. But there is no obvious reason why radiotherapy should not be applied in patients with FOP, taking into account its similar patophysiology with other forms of heterotopic ossification.

The rationale for use of radiotherapy in FOP clearly exists. The patient was informed about the possible risk of radiotherapy and treatment failure, and gave informed consent. This case might be considered as a unique case of successful radiotherapy in patient with FOP, specially considering that radiotherapy was delivered in many sessions, eight exactly, producing durable therapeutic response.

We have performed a search of PubMed database and found only two case reports in the literature on radiotherapy treatment of such patients, with a relatively short follow-up[12,13].

One refers to radiotherapy accompanied by indomethacin therapy after heterotopic bone excision in 18--year-old patient with the follow-up of one year. In this case, radiotherapy and indomethacin were given as a common prevention of ossification, assuming the regular onset of heterotopic ossification after bone surgery. Only a small amount of heterotopic bone formation was radiologically found at the operative site, one year after the surgery. The other is a case of radiotherapy reducing the femoral nerve compression in FOP patient with clinical and radiological improvement, revealed two months af-

ter the procedure. In both cases a single fraction irradiation was performed (7 Gy and 10 Gy respectively) and radiotherapy produced noticeable effect.

Except for these two anecdotal reports, there is no clear evidence the radiotherapy is effective in patients with FOP. However, there might be a rationale for small doses of radiotherapy treatment in FOP, since radiotherapy is efficient in proliferating cell kill and can induce bone remodelling, with no serious side-effects. Those two elements are crucial in pathophysiology of FOP lessions[14].

Since radiotherapy is not an established treatment for FOP, the most effective fractionation schedule is unknown. Using the evidence-based data, from a large body of literature regarding radiotherapy administered for preventing heterotopic ossification following total hip arthroplasty, it can be found that a total dose and dose fractionation schedule are still a matter of debate, with no specific treatment regime advocated[15].

Conclusion

As there is no effective treatment for FOP and bone surgery is contraindicated, radiation therapy should be considered, in specific cases, as the treatment of choice for patients with FOP, especially taking into account that radiotherapy is well tolerated treatment with no side-effects. This treatment should be tested in larger number of FOP patients to evaluate its actual efficacy.

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RADIOTERAPIJA U LIJEČENJU PROGRESIVNE OSIFICIRAJUĆE FIBRODISPLAZIJE: PRIKAZ SLUČAJA I PREGLED LITERATURE

SAŽETAK

Fibrodysplasia ossificans progressiva (FOP) vrlo je rijetki genetski poremećaj kojeg karakterizira difuzno ekstraskeletalno stvaranje kosti. Genetska mutacija odgovorna za nastanak FOP-a je nedavno otkrivena i povezana je s prekomjernom aktivnosti receptora za koštani morfogenetski protein. Ta bolest obično počinje u ranom djetinjstvu tipičnim načinom okoštavanja, uzrokujući progresivnu onemoćalost, tako da bolesnici postaju potpuni invalidi do dobi od 30 godina. Ektopično okoštavanje se razvija spontano i može biti uzrokovano bilo kakvom vrstom traume, čak i intramuskularnim injekcijama. Simptomi FOP-a se često krivo dijagnosticiraju kao rak, uzrokujući nepotrebne biopsije, što precipitira daljnje opsežno ektopično okoštavanje. Nema učinkovitog liječenja za ovo teško stanje. Radioterapija može biti korisna u usporavanju okoštavanja, iako nema čvrstih dokaza za to. Postoje samo dva literaturna izvještaja koji se odnose na korištenje radioterapije u liječenju FOP-a. U ovom radu prikazuje se slučaj 35-godišnje bolesnice koja je uspješno liječena malim dozama frakcionirane radioterapije. Ovaj slučaj upućuje na činjenicu da radioterapija može biti korisna u liječenju bolesnika sa FOP-om.