Osteoarticular changes in Refsum's disease: a case report

Marcin Bednarek (marcin.bednarek@uj.edu.pl)
Jagiellonian University Medical College
Maciej Belka
Jagiellonian University Medical College
Małgorzata Grudniewska
Jagiellonian University Medical College
Łukasz Pawliński
Jagiellonian University Medical College
Artur Gądek
Jagiellonian University
Beata Kieć-Wilk
Jagiellonian University Medical College

Case Report

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Abstract

Background

Refsum's Disease (RD) is a rare and complex disease of lipid metabolism with the domination of neurological symptoms and impacting the metabolism of phytanic acid. The metabolic block, inherited in an autosomal recessive manner, affects the growth and functioning of the myelin sheath around nerve cells. Approximately 35% of RD patients have changes in their osteoarticular system. The most common anomalies are shortening and deformity of many tubular bones in the hands and feet. Over time, chronic, progressive, symmetrical, and mixed motor-sensory polyneuropathy develops, initially involving the lower limbs, and later, the upper limbs. It leads to muscle weakness and walking disorders. Prevalence rates are not known but RD may be under-diagnosed.

Case presentation

We report an interesting case of a 49-year-old woman with symmetrical bone anomaly in the feet and hands, diagnosed with RD. Though she had the changes typical of RD since childhood, she was not diagnosed until her 40s, once serious complications of RD appeared.

Conclusions

Early diagnosis of RD is essential for implementation of effective treatment to significantly improve quality of life of the patient. We should always consider running expanded diagnostics, including genetic tests, with patients presenting with bone changes typical for RD. The interdisciplinary approach from different specialists is the key to reduce symptoms and complications. The factors influencing the development of bone, joint, and muscle anomalies in RD are still unknown.

Background

Refsum's disease (RD), a hereditary motor-sensory neuropathy type IV, is one of the rarest leukodystrophies and is caused by disturbed lipid metabolism. This genetically determined metabolic block, inherited in an autosomal recessive manner, affects the growth and functioning of the myelin sheath around nerve cells [1–4]. The most common cause of RD is a mutation in the phytanoyl-CoA 2-hydroxylase (*PHYH*) gene coding for an enzyme located in peroxisomes, which is necessary for the metabolism of phytanic acid, a metabolite of phytol and a component of chlorophyll. The PYTH metabolic block causes the gradual accumulation of phytanic acid in the blood plasma and tissues [4–5]. Progressive damage most often affects the central nervous system and sensory organs. Clinical symptoms usually appear before the age of 20 but may also appear in the 5th decade of life [3,7]. The most common, and often earliest symptom, is visual disturbance related to retinal degeneration or dystrophy in adults during the course of retinitis pigmentosa, which often becomes apparent in childhood. Additionally, up to 50% of RD patients are diagnosed with night blindness, visual field limitation, or cataracts [3]. Although it does not appear to be the earliest symptom, in 80% of patients

diagnosed with RD, sensorineural hearing loss has been reported, gradually leading to deafness, as well as anosmia and ichthyosis [7,8]. One of the later symptoms is cerebellar ataxia. Over time, chronic, progressive, symmetrical, mixed motor-sensory polyneuropathy develops, initially involving the lower limbs, and later the upper limbs [1,3]. This condition leads to muscle weakness and, subsequently, gait disturbance. In individual cases, it contributes to the formation of hollow foot deformities (pes cavus) and other anomalies within the skeletal system. Although neurological symptoms dominate the disease picture, it is estimated that changes within the osteoarticular system occur in approximately 35% of RD patients [9]. The most common anomaly is shortening of the 4th bone of the foot, which occurs symmetrically. Long bone dysplasia and osteophytes in the epiphyses of the long bones may appear, mainly in the area of the knee, elbow, and shoulder joints [1,3,5,6,9,10]. Additionally, some patients with RD develop cardiac arrhythmia and heart failure, caused by cardiomyopathy, that can be life-threatening [1,3,6,11].

RD is treatable because phytanic acid is not produced by the body and can be significantly reduced with dietary changes. With treatment, the neurological symptoms such as muscle weakness and numbness, and the dry and scaly skin, generally disappear. However, more severe symptomatology such as vision and hearing problems may persist, and sense of smell may be disturbed [12,13]. It is important to keep in mind that untreated RD can lead to sudden death caused by heartbeat abnormalities.

Interestingly, the prevalence of RD is unknown, although the condition is thought to be very rare. No exact estimates of RD prevalence are known. Until now, most cases described in the literature have been from the United Kingdom and Norway, likely due to a higher awareness of this disease in those countries [14]. To the best of our knowledge, the number of RD cases in Poland has not been estimated, and only 2 cases in Poland have been described so far [15,16]. This paper presents a new case of an RD patient in Poland. As the bone anomalies are rarely described in the literature, our aim is to focus on osteoarticular changes in our patient.

Case presentation

A 49-year-old woman was referred by a rare disease specialist to our out-patient clinic for an orthopaedic consultation due to knee pain and muscle weakness. A few months earlier, she visited the ophthalmologist due to problems with her eyesight. The ophthalmologist diagnosed retinitis pigmentosa and referred her to a clinical genetic specialist, due to suspicion of RD based on the changes he observed in the retina. The genetic specialist confirmed this suspicion of RD with a positive molecular test. Additionally, the phytanic acid level was elevated up to 600 μmol/l. Her family history revealed that her parents were not related, came from different regions of Poland, and that her father had not been diagnosed with RD; however, he had been treated for glaucoma and visual disturbances. In addition, the patient's aunt (father's sister) had changes in her feet typical of RD, but she did not consent to the proposed expanded diagnostics. During the physical examination of our patient, we found symmetric developmental anomalies in her hands and feet, that had been present since early childhood. Shortening

of all digits was noticeable, especially within the feet. Additionally, there was shortening and dorsal subluxation of the fourth toe and syndactyly of the second and third toes (Figure 1 - 2A, B). The range of active and passive movement in the joints of the upper and lower limbs and in the spine was within the normal range. A gait disturbance was not detected. Furthermore, upper and lower limb muscle strength and tension were symmetrical, but slightly weakened.

The radiograph of the feet (AP and side view) showed bilateral and symmetrical hypoplasia of the 4th metatarsal bones, probable hypoplasia of the middle and distal phalanx of the 4th toe, and hypoplasia of the basal phalanges of both first toes. Thinning of the bone shafts of the 2nd-4th metatarsals and the 3rd-5th proximal phalanges of the toes was also detected. Additionally, enlargement of the distal end of the 2nd-5th metatarsals, hypoplasia of the proximal end of the 1st and partially 2nd proximal phalanges of toes, and ankylosis of the distal interphalangeal joint of the 5th finger were diagnosed (Figure 3 A - C).

In imaging studies, comparative X-rays and lateral projections of the hands revealed bilateral and symmetrical hypoplasia of the 1st and 5th metacarpals, thinning of the 2nd-4th metacarpal shafts, hypoplasia of the middle phalanx of the 5th finger with hypoplasia of the distal phalanx of the thumb, and a positive ulnar variant- the distal articular surface of the ulna was more distant than the radial surface (Figure 4A). Moreover, bilateral and symmetrical scaphoid hypoplasia and dorsal ulna subluxation at the distal radioulnar joint (DRUJ) were diagnosed (Figure 4A - B).

Due to complaints of pain from the patient, radiological diagnostics were extended. The pelvic radiograph (AP projection) showed bilateral degenerative changes of the hip joints presenting as joint space narrowing with excessive sclerotization of the acetabular roofs, with acetabular-cervical conflict. Moreover, there were valgus deformations of both femurs with a neck-molar angle of 140°. Additionally, there were slight degenerative changes in the sacroiliac joint and the pubic symphysis (Figure 5).

A comparative radiograph of the knee joints showed bilateral degenerative changes in the form of sclerotization of the subchondral articular surface of the tibia and femur, especially in the medial compartment. There were osteophytes that narrowed the articular spaces, especially in the medial compartment. Moreover, sharpening of the medial cusps of the intercondylar eminence of the tibia was detected. Additionally, there was an asymmetric, clinically silent osteophyte on the lateral surface, indicated by the left arrowhead (Figure 6).

Among the additional symptoms, the patient also reported muscle weakness in the limbs, mainly in the forearms, hands, lower legs and feet, and periodically she experienced diffuse pain, occasionally manifesting above the hip and knee joints. Besides osteoarticular changes, our patient had other symptoms of RD, such as ichthyosis located on the head and neck, which gradually worsened over time. Furthermore, the visual disturbances began in childhood- mainly night blindness. When she was 11 years old, astigmatism was diagnosed, and at the age of 45, a colour vision disorder appeared. Retinal dystrophy during the course of retinitis pigmentosa and posterior subcapsular cataract in the initial stage were diagnosed recently in 2020. The rapid progression of her eye lesions prompted the attending physician to carry out an extended genetic diagnosis focusing on rare congenital eye diseases. The high-

throughput sequencing NGS method was used for this purpose, and compound heterozygosity for the *PHYH* gene was detected, consisting of pathogenic mutations: nonsense c.364C> T (p. Gln122Ter) and a sense shift mutation c.763A> C (p. Thr255Pro). Based on the genetic results, Refsum's Disease was diagnosed.

An important ailment reported by the patient was self-limiting tachyarrhythmia attacks, caused mainly by stressful situations, over the last 10 years. There were no significant abnormalities in the 24-hour ambulatory ECG, apart from additional supraventricular beats, which amounted to approximately 190 per day, within the reference range. The ECHO examination revealed hypokinesis of the basal segment of the inferior wall and the posterior part of the interventricular septum of the heart, with normal left ventricular ejection fraction and fibrosis of the mitral valve leaflets but without stenosis or regurgitation.

The patient is currently being treated with ascorbic acid, a diet with limited consumption of phytic acid and its precursor phytol, and she does not require orthopaedic intervention.

Discussion and conclusions

Sigvald Bernhard Refsum (1907–1991) first described RD, based on four cases of two unrelated Norwegian families in 1945. He named it heredopathia atactica polyneuritiformis [1,6,10,11]. The frequency of this disease is not exactly known and it is underestimated. Some sources show frequencies ranging between 1/1000000 and 1/250000, but most authors confirm the lack of accurate data for estimating the epidemiology of this disease [3,17,18].

Most studies present genetic aspects or disturbances in metabolic pathways and discuss individual cases of patients or families suffering from RD. Due to the diversity and dominance of symptoms from sight, hearing, organs, and nervous system, bone developmental anomalies are rarely described in these patients [3, 19–21]. However, bone changes were described by Refsum [6]. He observed hypoplasia and dysplasia of the long bones of the hand and feet, as well as dysplastic changes in the epiphyses of the long bones forming the knee, shoulder and elbow joints. Even in the 1960s, it was believed that bone changes occurred in 50% of patients, and when degenerative changes of joints were included, this percentage increased to 75% of patients with RD [9]. Finally, after 30 years, it was determined that bone anomalies of the hands, feet, and knee and elbow joints occurred in 35% of patients [9].

Dysplasia of the epiphyses of long bones usually develops symmetrically and bilaterally. In addition, these types of changes occur mainly in the bones forming the large joints of the limbs, such as the knee, shoulder, or elbow [2,5,9–11,22]. Dysplasia of the distal part of the humerus was described in 50% of RD patients as flattening of the lateral part of the trochlea [9]. In contrast, developmental anomalies of the femur presented as an inverted letter V with flattening of the medial and lateral condyles, irregular subchondral layers, and marginal osteophytes [10]. Similar changes, but more advanced, were found in our patient and were most likely related to the patient's age, with a longer-lasting disease process overlapping natural degenerative changes. To date, only one study has described degenerative changes within the hip

joints in patients with RD [23]. However, we did not observe degenerative changes in the sacroiliac joints or the pubic symphysis in our patient. Interestingly, we did not find dysplastic changes in the bones of her shoulder joint, which have often been described in previous studies [9].

The anomalies of the hand and foot bones were presented by Reese and Baret in 1950 [24]. In the described patients, symmetrical, bilateral dysplastic lesions were found within the fifth metacarpal bone as a thickening of the shafts and a distortion of the distal articular surface together with shortening of the 4th middle phalanx and 4th distal phalanx [10]. Hypoplasia of the 4th metatarsal bone was most common in the foot area. These changes can also affect the remaining metatarsal bones, as well as the phalanges of the toes. In the studied group of patients, Wall observed symmetrical bilateral dysplastic changes with shortening and dorsal flexion of the 3rd metatarsal bone, as well as shortening of the 4th metatarsal bone, proximal phalanx of the 4th finger and phalanges of the toes [10]. Similar changes within the long bones of the feet and hands were presented by Plant, but in approximately 17% of patients they only appeared on one side [9]. This type of bilateral developmental anomaly in the feet and hands was found in our patient.

A gradually developing mixed peripheral neuropathy first affects the lower and then later the upper limbs, symmetrically. It leads to weakness and atrophy of the muscles. These changes are manifested by foot drop and weakness and, in an advanced form, by the disappearance of tendon reflexes. The loss of sensation is progressive and leads to its total disappearance in the distal parts of the limbs (socks and gloves syndrome). Changes in the structure and functioning of muscles lead to the development of incorrect posture and gait disturbances (the so-called atactic gait). In some patients, progressive polyneuropathy leads to the formation of a hollow-type foot deformation (pes cavus) [2,11,21,25]. In our patient, polyneuropathy caused a reduction in peripheral sensation and a weakening of the muscle strength of the upper and lower limbs.

In some of the studies, we found less typical changes within the osteoarticular system diagnosed with X-ray examinations, such as osteochondrosis of the medial femoral condyle, spondylopathy of the cervicothoracic spine, and an enchondroma of the proximal end of the proximal phalanx of the 4th left finger [2]. It seems that the described "RD atypical" changes are not directly related to the underlying disease and may arise during the course of aging (spinal spondylopathy) or occur independently and randomly (enchondroma).

Studies on the pathomechanism of changes during the course of Refsum's disease concern disturbances of peroxisome function in the process of alpha-oxidation of fatty acids and secondary beta-acid oxidation problems, and the intensification of cell apoptosis and abnormalities of nerve cell functions [43]. However, we do not know the precise pathomechanisms leading to the development of congenital bone disorders in the course of RD. The ongoing discussion is concerned with whether the observed bone changes are congenital or acquired. There is no evidence as to whether these pathologies were present from birth or developed with age. Doubts are raised by the fact that in foetal life, the level of phytanic acid

in the foetal blood is zero [9]. Studies in animal models have shown the negative effect of increased phytanic acid concentration on the levels and action of growth factors, mainly regulating vascular growth and maturation [43]. Research on other diseases found epigenetic factors that contribute to bone modification. Changes in epigenetic mechanisms as well as intercellular transmission (miRNA) occur throughout the entire body. It seems appropriate to undertake research on the analysis of changes at the protein level to investigate its role in the processes of destruction and regeneration of bone tissue regulated by specific miRNAs. Future research in this direction will allow for the assessment of new molecular mechanisms determining organ changes in the course of RD. The obtained results may help to explain and understand the pathophysiology of bone complications in patients with RD.

The factors influencing the development of bone and joint anomalies in RD, why they most often occur in the long bones of the feet and hands, and dysplasia in the bones forming large joints, e.g., knee and elbow joints, are still unknown. This disease definitely requires further observation and research. A patient with RD needs to be managed by a multidisciplinary team, including genetic specialist, ophthalmologist, neurologist, rare disease specialist, cardiologist, dermatologist, dietician and orthopaedic specialist. Early treatment may reduce the symptoms and significantly improve the quality of life of patients.

Abbreviations

AP– anterior-posterior, DRUJ- distal radioulnar joint, ECG- electrocardiography, ECHO- echocardiogram, mi-RNA- micro Ribonucleic Acid, NSC- next generation sequencing, PHYH- phytanoyl-CoA 2-hydroxylase, RD- Refsum's Disease

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The written informed consent for publication has been obtained from the patient.

Availability of data and materials

This is a case report of a single patient, to protect privacy and respect confidentiality. The original reports, laboratory tests, imaging and outpatient clinic data are retained as per standard procedure within the medical records of our institution.

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MB consulted the patient regarding osteoarticular changes, was a major contributor in writing the manuscript and approved final version.

MacB wrote the initial draft of these article.

MG helped in writing the manuscript and consulted the patient regarding the diet as a dietician.

LP analyzed and interpreted the patient data regarding RD

AG performed revisions regarding osteoarticular changes.

BKW supervised the article as a rare disease consultant.

All authors have read and approved the final manuscript.

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Figures

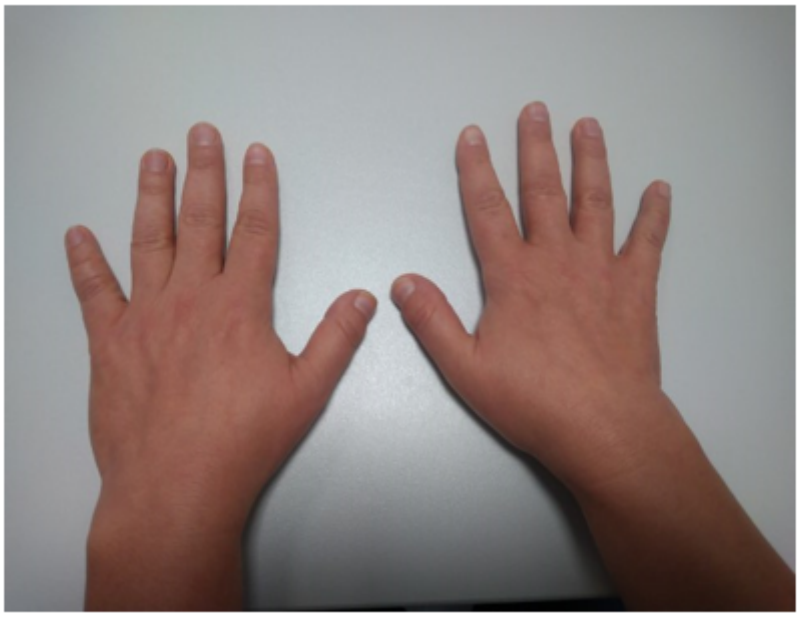
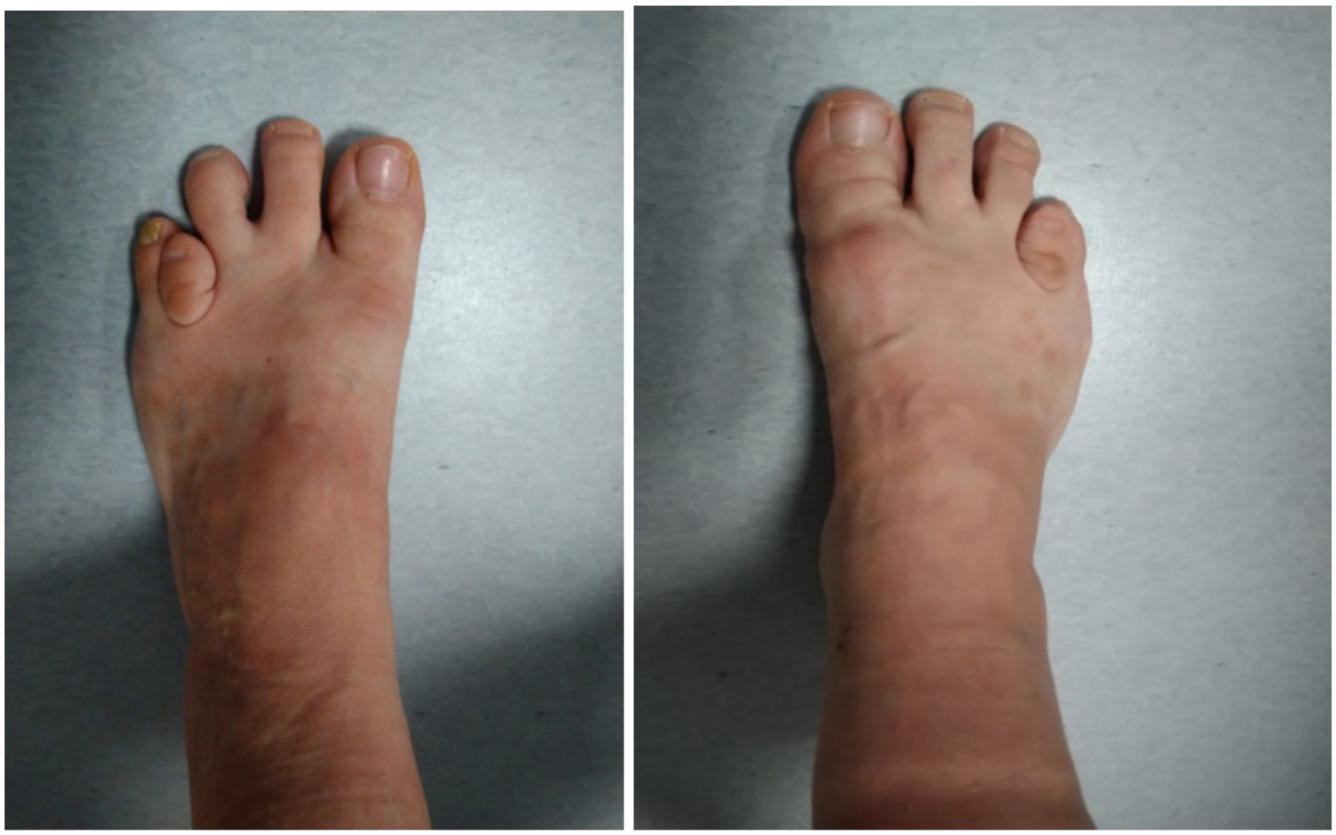


Figure 1

Comparative picture of the hands (dorsal surface)



A B

Figure 2

Comparative photo of the feet (dorsal surface): A - left foot; B - right foot

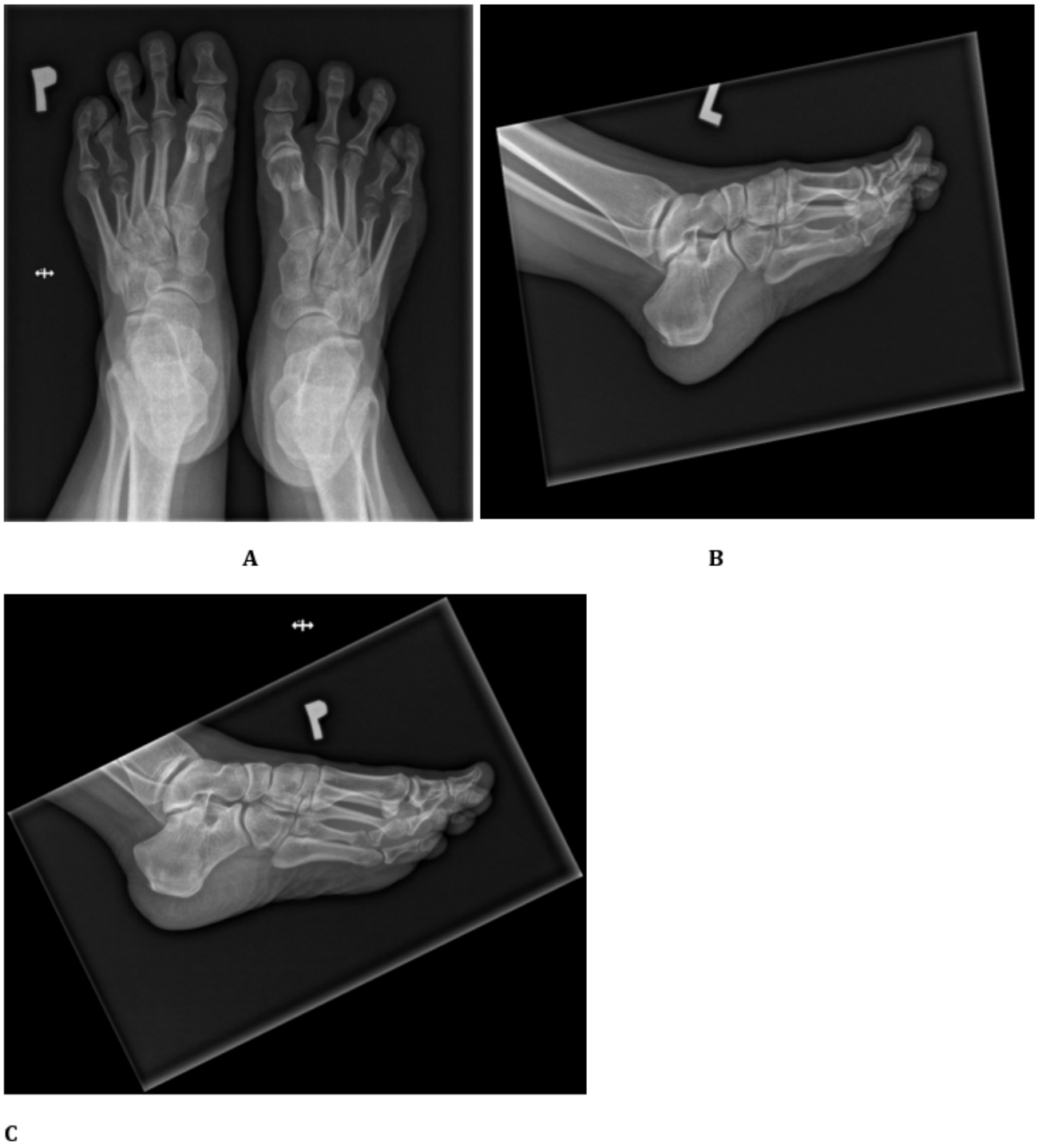


Figure 3

X-ray of the feet: A) comparative AP image; B) X-ray of the left foot (lateral projection) C) X-ray of the right foot (lateral projection)

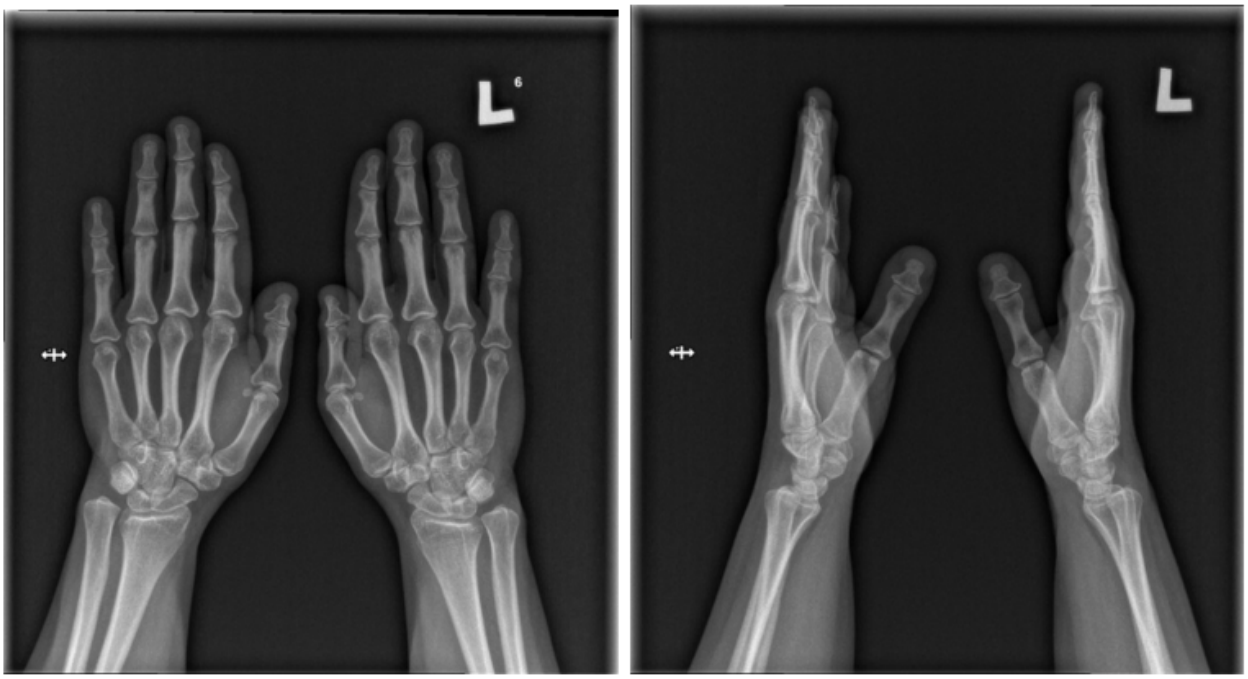


Figure 4

X-ray of the hands with the wrists and 1/3 of the distal forearms A) comparative AP image, B) lateral projections

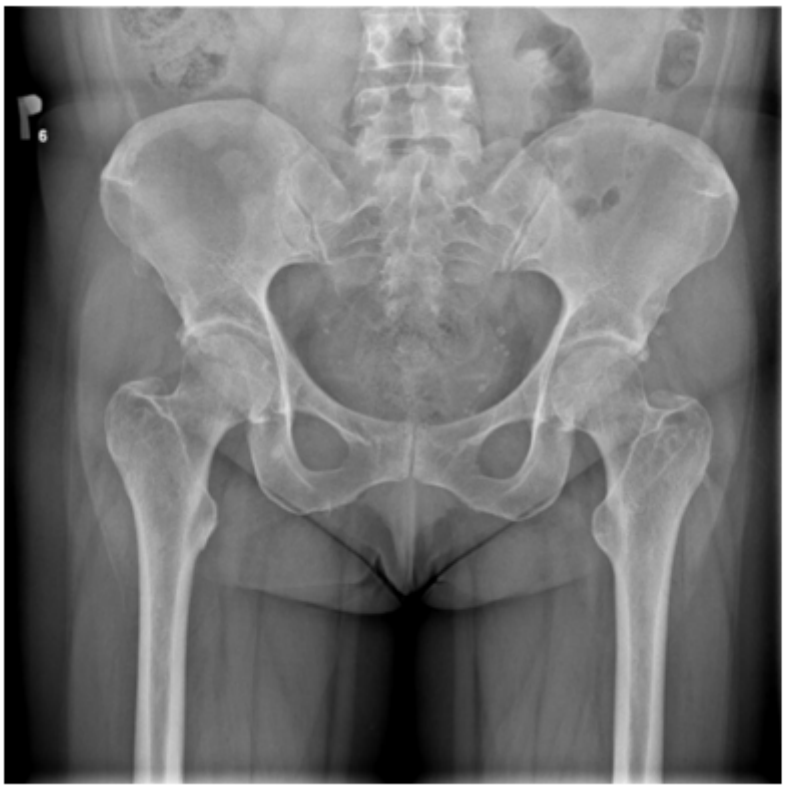


Figure 5

X-ray of the pelvis and 1/3 proximal femurs (AP view)

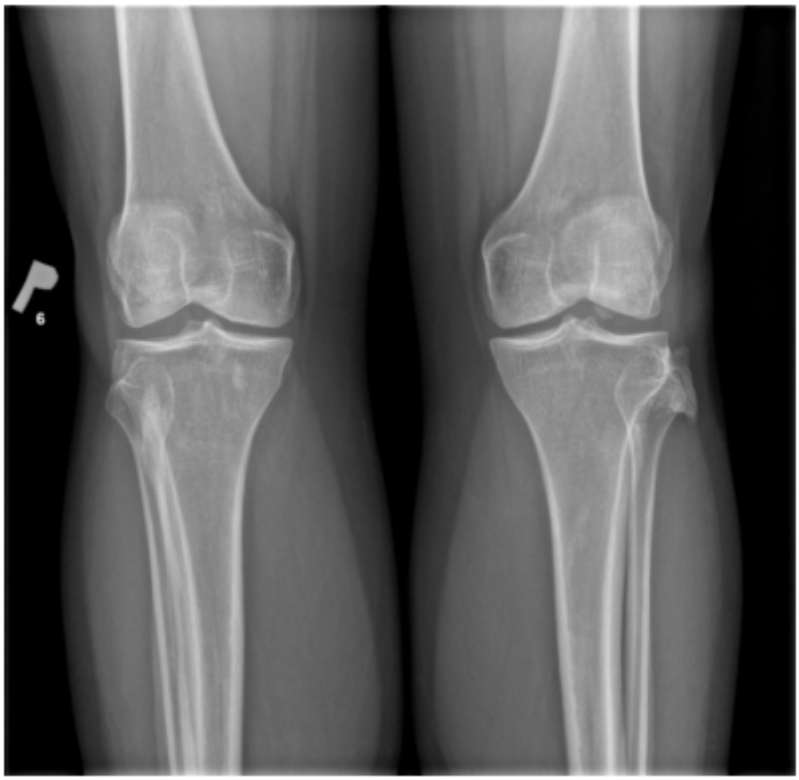


Figure 6

Comparative X-rays of the knee joints and 1/4 of the distal femurs and 1/3 of the proximal lower legs.