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Title

Orthopaedic aspects of SAMS syndrome

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Abstract

The combination of Short stature, Auditory canal atresia, Mandibular hypoplasia, and Skeletal abnormalities (SAMS, OMIM 602471) has been reported as a very rare, autosomal-recessive developmental disorder with unique skeletal anomalies. Up to now only four patients have been reported. There are a number of striking orthopaedic diagnoses within the SAMS syndrome. In particular the scapulohumoral synostosis and the bilateral congenital ventral dislocation of the hips. Whenever a bilateral congenital ventral dislocation of the hips and or a scapulohumoral synostosis is found or clinically suspected, SAMS syndrome should be considered as primary diagnosis until proven otherwise.

Introduction

The combination of Short stature, Auditory canal atresia, Mandibular hypoplasia, and Skeletal abnormalities (SAMS, OMIM 602471) has been reported as a very rare, autosomal-recessive developmental disorder with unique skeletal anomalies. These include bilateral humeral hypoplasia, humeroscapular synostosis, pelvic abnormalities, and proximal defects of the femora.[1] Up to now only four patients have been reported.[2,3]

SAMS was reported in two cases to be a provisionally autosomal-recessive disorder with features of a first and second branchial arch syndrome. [1,2] However, these two patients (Patient A and B) also had additional, unique skeletal anomalies that comprised bilateral humeral hypoplasia, humeroscapular synostosis, pelvic abnormalities and proximal defects of the femora. Those cases were further elaborated in the article of Parry et al, and uniquely extended to a total of four patients with the same clinical features.[3] The genetic origin was discovered in patient C by exome sequencing to be an homozygous predicted null mutation of GSC, encoding Goosecoid homeobox protein, a paired-like homeodomain transcription factor. In patient A, a homozygous 306 kb microdeletion including the Goosecoid gene only, confirmed that SAMS is a human malformation syndrome resulting from GSC mutations.[3]

There are a number of striking orthopaedic diagnoses within the SAMS syndrome. This article will elaborate on the orthopaedic aspects of the SAMS syndrome, of all known patients to date with SAMS syndrome. A differential diagnosis and subsequent treatment recommendation is provided where possible. Informed consent was obtained from all individual participants included in the study.

SAMS Population

Patient A

This female was first seen by clinical genetics at 9years of age. She is the youngest of six children born to consanguineous (first cousin) Caucasian Mennonite parents. Her five older sibs and her parents are all phenotypically normal. She was born at term in to a 32-year-old mother and a 37-year-old father. She sat at 9 months, walked at 19 months, spoke her first words at 24 months, and talked in sentences by 5 years. Continence was achieved during the third year. Her psychomotor development was delayed. At birth, bilateral atresia and short humeri with restricted shoulder movement was noted. The family emigrated to Canada from Mexico when she was a young child. At nine-years-old she was functioning as an average student at a grade 2 to grade 3 level. On physical examination she presented as a small for her age child with an unusual facial appearence. There was hypotelorism with deeply set eyes and downslanting palpebral fissures, malar hypoplasia, micrognathia and a small mouth with prominent upper central incisors. She had a high-arched palate with crowding of teeth and a short frenulum. The ear pinnae were simple and dysplastic; both ear canals were atretic. Humeri were short with winged scapulae and a lumbar hyperlordosis. her range of motion of both shoulders were markedly restricted, all motion was due to scapulothoracic movement. Some degree of flexion contracture was noted at the hips and the feet (described below) easily rolled into valgus. Skeletal radiographs showed severe mandibular hypoplasia, bilateral scapulohumeral fusion, short humeri with some distal metaphyseal flaring. There was a metacarpal sign on the right and mild shortness of the ulnae. Height was 107.5 cm, weight 15 kg, and OFC 49 cm (all $<5^{th}$ centile). The carpal length was very short, about three standard deviations below the mean for chronological age. Complete failure of

ossification of both pubic bones and the very small sacro-sciatic notches are evident on the radiograph. Both hips were ventrally dislocated. The proximal femoral epiphyses were very poorly ossified, and slightly irregular and flattened; the femoral necks were short and wide. There was a mild degree of ‘‘ball in socket’’ deformity of both ankle joints, and the ossification centers for the calcaneal apophyses appeared unusual.

She was re-evaluated at 26 years of age. She was employed as an office assistant. She is single lives with her older sister and family. She seems socially well developed, has a driver's license and has hobbies that include crochet, floral arrangements and she does belong to a church group. Currently, she uses an amplified hearing system because of her conductive deafness. She has had dental work, but no surgery on her jaw. She has no visual problems, but she does complain of headaches related to the computer work. She does have regular periods it is likely she is likely to be fertile but she has never had a pregnancy. She cannot raise her arms above her shoulders because of the scapulohumoral fusion. In addition, she complains of hip pain. This is aggravated by standing for a long time, walking for long distances or sitting in one place for too long. She takes occasional Advil and Tylenol for the pain. An orthopaedic evaluation in her small rural community revealed bilateral hip dislocation. Radiographs of her pelvis showed “no acetabulae”.

On examination, her height is 4 feet 8 inches tall. Her weight is 82 pounds and her head size was 52.5 cm (<5th percentile). She has a small face, a high arched palate with some teeth crowding and a small mandible. Her ears externally appeared normal except that she has no ear canals. She has a marked lordosis but no obvious scoliosis. Her forearms and hands appeared normal, but she has restricted supination of the forearms. She also cannot lift her

arms above her shoulders. Hip abduction was restricted. She walked with a waddling gait consistent with severe hip disease.

Patient B

A Currently twenty-one-year-old female was the fifth child born to consanguineous (first cousins) Afghan parents. At birth, bilateral auditory canal atresia, short humeri, and clubfeet were noted. She had simply-formed external ears with bilateral auditory canal atresia, with a conductive hearing loss of 40 dB. There was severe micrognathia but no cleft palate. The humeri were short with winged scapulae. All motion of the shoulder was due to scapulothoracic movement. She had clubfeet and normal hips. At the age of 5 years psychomotor development and behavior were appropriate for age. The clubfeet were treated with casts and she underwent multiple orthopaedic surgical procedures that enabled her to walk with orthopaedic adjusted shoes. The surgical procedures were performed in the country of origin, unfortunately no specific details are noted. She had a restricted range of motion of both shoulders and luxations of the proximal radius. Skeletal radiographs showed very striking findings; there was severe mandibular hypoplasia, bilateral scapulohumeral synostosis, and there were no distinct humeral heads recognizable. The humeri were broad and short. Both elbows showed lateral dislocation of the radius. Both hands had proximally implanted thumbs. Delayed ossification of both pubic rami and large sacro-sciatic notches were present. Both hips were ventrally dislocated, and internally rotated (Figure 1). Both feet were fixated in endorotation. Currently height is 157 cm (3rd centile) and weight 42 kg (2nd centile). Walking is possible with use of orthopaedic adjusted shoes, without use of

crotches. Although the hips are both ventrally dislocated and minimized in their motion, there are minimal complaints of discomfort.

Patient C

A currently seven-year-old male was born at 34 weeks of gestation by emergency caesarean section for fetal distress and failure to progress after an uneventful pregnancy with normal scans. The birth weight was 1.95 kg, which is in the second centile, and the occipitofrontal circumference was in the 91st centile. Initial and subsequent postnatal examinations revealed a high-arched palate, malar hypoplasia, and severe micrognathia leading to respiratory compromise. He appeared to have rhizomelic shortening of upper limbs, and reduced pronation /supination of elbows with proximally placed thumbs. He also had bilateral fixed clubfeet with reduced calf bulk, bilateral cryptorchidism, rudimentary pinnae, and bilateral external auditory canal atresia. An auditory brainstem response test was performed at a corrected gestational age of 8 weeks and revealed that both sides were measured at less than 30 dBnHL. Other dysmorphic features included scaphocephaly with a prominent forehead; a slightly downward slant to the palpebral fissures; a short, upturned nose; and a small mouth. In contrast to individuals A and B, individual C had severe neonatal respiratory insufficiency necessitating a tracheostomy and nasogastric feeding because of poor coordination with no suck, swallow, or gag. A skeletal survey of individual C revealed left humeroscapular synostosis, a feature that appears to be pathognomonic for SAMS, but the right shoulder joint appeared normal. There was flaring of the distal metaphysis, immature ossification of the pelvis and resulting flattened acetabulum and bilaterally dislocated hips. There was bilateral shortening of clavicles and absence of ossification of the

pubic rami. The spine appeared normal. His clubfeet were initially managed by serial Ponsetti casting, and at the age of 2 months the patient underwent bilateral percutaneous achilles tenotomies followed by serial casting. Currently the patient has gone over to ankle-foot orthoses.

Patient D

A currently 3½-year-old male was the first child born to consanguineous UK-Bangladeshi parents. He was born at 34 weeks of gestation with a birth weight of 2.25kg after prolonged rupture of membranes at 32 weeks. At birth, bilateral auditory canal atresia, rhizomelic shortening, talipes requiring physiotherapy and a flat perineum were noted. Like individual C, he required support with feeding, with a gastrostomy inserted at the age of 8 months. He sat independently at 18 months and walking with a frame age 2½. At 3½, he has several single words but communicates mainly through pointing. Initial and subsequent examination revealed a small boy with micrognathia and downslanting palpebral fissures. His ears were simple, low-set and posteriorly rotated. There was crowding of teeth and a high palate. There was a tendency to hold arms in flexion and internal rotation and there was limited rotation in both forearms and limited abduction of both hips. Skeletal X-rays demonstrated bilateral scapulohumeral synostosis with mild scapular hypoplasia and bilateral radial head dislocation. The inferior pelvis consisted of paired single bones, though to reflect ischial rami and tuberosities, with no ischial body or pubic ossification. There was no femoral head ossification and the upper femora articulated with the inferior iliac bones. The femora were markedly internally rotated, with greater trochanters facing medially. Frog leg lateral views showed adequate anteversion.

A detailed MRI evaluation of the pelvis at the age of 22 months. This clarified some of the unusual anatomical features: the inferior pelvis comprised a short ischiopubic ramus with morphology suggesting the presence of an ischial tuberosity, conjoined ischial and pubic rami, and small pubic bodies, with abnormal fusion of the pubic bodies. The bodies of the ischia, including the ischial spines, were completely absent (no bone or cartilage present), as were the superior pubic rami. There was no bony or cartilaginous connection between the small ischiopubic rami and the iliac bones; a musculo-tendinous structure stretching from the medial iliac bone to the ischiopubic ramus was present. This may represent an abnormal obturator internus. In essence, there is no acetabulum. The upper femora demonstrated very small, flat, unossified cartilaginous epiphyses, articulating with the inferior iliac bone only.

Discussion

The clinical features in 4 patients with SAMS syndrome are reported. The various striking orthopaedic features are enumerated in the below.

Bilateral congenital ventral hip luxation

Subluxation of the hip is an incomplete contact between the articular surfaces of the femoral head and acetabulum, whereas dislocation represents a complete loss of contact. The femoral head can dislocate either posterior-laterally (dorsal) or anterio-laterally (ventral). Whilst earlier reports on SAMS have not clearly defined the direction of the dislocation or subluxation of the hip, we suggest that anterior dislocation is the typical

feature associated with SAMS (Figure 1). To the best of our knowledge, bilateral – congenital- ventral dislocation of the hip is, apart from the previous articles describing SAMS syndrome, not mentioned before in current literature.

There are several conditions that feature bilateral posterior congenital hip dislocation. The first report describes occurrence of bilateral hip dislocation in Ehlers-Danlos syndrome (EDS, OMIM 130000-130090).[4,5] The association of congenital joint dislocations and EDS has only been reported in Types I and VII.[4] In all patients, the diagnosis of congenital hip dislocation was made remarkably late, in seven of nine because of a limp when walking**.**

The second condition with bilateral posterior hip dislocation is the pseudoaminopterin syndrome (OMIM 600325); fetuses exposed to aminopterin during the 8^{th} – 9^{th} week of development may show aminopterin embryopathy, resulting in a specific phenotype that includes unusual face, skull, and skeletal abnormalities.[6]

A third condition describing posterior bilateral hip dislocation is nail-patella syndrome (OMIM 161200). Nail–patella syndrome (also known as "HOOD syndrome") is a genetic disorder that results in small, poorly developed nails and kneecaps, but can also affect many other areas of the body, such as the elbows, chest, and hips. Mentioned only once in current literature, this is a rare symptom within the nail-patella syndrome.[7]

The fourth syndrome describing bilateral posterior hip dislocation is Larsen syndrome (OMIM 150250). Larsen syndrome is a rare pathologic condition characterized by congenital multiple joint dislocations, most striking the knee dislocations, with characteristic facial features.[8] The fifth condition affecting hip development is arthrogryposis (eg distal arthrogryposis as OMIM 108120). Arthrogryposis represents a group of heterogeneous disorders, characterized by contractures of multiple joints at birth. Involvement of the hip is

very common (55-90% of patients) ranging from soft tissue contractures to subluxation and dislocation. Congenital posterior bilateral dislocations are frequently described within the spectrum.[9] Finally, spina bifida (OMIM 301410) can result in bilateral posterior hip luxation. Children with spina bifida develop a wide variety of congenital and acquired orthopaedic deformities. Among these are hip deformities such as contractures, subluxation and dislocation.[10]

As with most patients with (bilateral) luxated hips, if permitted within the syndromal range, SAMS patients are able to walk. As seen in Figure 1; a neojoint has developed over the trochanter majus to the posterior acetabular rim, which allows for weight bearing. Treatment (or management) of the dislocated hips in SAMS depends largely on the individual anatomical situation. In the absence of an acetabulum, a hip joint cannot be reconstructed and a conservative approach is warranted. The role of an acetabular of femur osteotomy depends on the individual situation and clinical symptoms that would limit physical function or health-related quality of life.

Scapulohumoral synostosis

Another very rare orthopaedic aspect of SAMS is the (bilateral) scapulohumoral synostosis. There are different syndromes featuring a limited shoulder function or cartilaginous disease of the shoulder causing shoulder impairment at older age. To the best of our knowledge there are no previous reports of a scapulohumeral or glenohumeral synostosis. The scapulohumoral synostosis is bilateral in all cases, except for patient C in whom only the right shoulder appeared normal (Table 1). In general when a restriction of motion is present in a large joint there should be a differentiation between primary osseous fusion or secondary changes that withhold some type of retriction of movement. In case of secondary

changes that restrict the scapulohumoral motion in a child, heterotopic ossification diseases such as progressive osseous heteroplasia (POH, OMIM 166350), Albright's hereditary osteodystrophy or McCune Albright syndrome (OMIM 103580) and fibrodysplasia ossificans progressiva (POH, OMIM 135100) should be considered. Initial radiographic exams will be able to exclude these differential diagnostic considerations.[11] Treatment is not possible in case of primary fusion, as there is no cartilage present. At most, an osteotomy of the upper arm can be considered when a problematic position is perceived. Treatment in case of heterotopic ossification diseases is controversial, as resection of the ossifications can lead to aggravation of the disease.[5,11]

Congenital radial head luxation

Bilateral radial head dislocation was noted in patient B and C, however not in patient A. (Table 1). Patient D was 9 months old at time of screening, it is unclear whether bilateral radial head dislocation will evolve in the near future. As most common congenital anomaly of the elbow, radial head dislocation has an estimated incidence rate of 0.06% to 0.16%.[12] Dislocations are most commonly posterior, with anterior or lateral dislocations present in one-third of cases. In most cases, congenital dislocation of the radial head is seen in conjunction with genetic syndromes such as Nail – Patella syndrome (OMIM 161200), Arthrogryposis (OMIM 108120), Apert syndrome (OMIM 101200) and Ehlers – Danlos syndrome (OMIM 130000-130090). Furthermore, posterior dislocations may show an autosomal-dominant or X-linked recessive mode of inheritance. Although it is most often bilateral, unilateral congenital radial head dislocation has been described.[12] Conservative treatment is indicated for the majority of cases because functional impairment is usually

minimal. However, in the setting of severe pain or restricted motion, radial head resection can be performed in skeletally mature patients. The procedure is contraindicated in children with open epiphyses because the radial head will regrow (and redislocate) following resection.[13]

Delayed ossification of the pubic rami

Delayed ossification of the pubic rami was noted in all patients, varying between slow ossification and complete absence. Wide interpubic distance is typical of conditions with defective and/or delayed ossification, such as achondrogenesis (OMIM 200600, 200610, 600972), hypochondrogenesis (OMIM 200610), spondyloepiphyseal dysplasia congenital (OMIM 183900) and opsismodyspasia (from Greek, delayed maturation; OMIM 258480). The most delayed pubic growth can be seen in cleidocranial dysplasia (OMIM 119600), in which hypoplastic pubic bones with wide pubic symphysis may persist until adulthood.[14] Although the delayed ossification has almost no clinical consequences, it can be seen as a predictor of certain processes at an early stage. In the neonatal period – an age when the clinical manifestations are ill- delayed ossification of the pubic rami can be an outstanding radiological finding. Correct evaluation and correlation can orient and define the diagnosis of certain processes at an early stage.[15] There is no treatment necessary.

Short humeri with distal metaphyseal flaring

Short humeri with distal metaphyseal flaring were present in three out of four patients. As short humeri are common within development of several forms of achondroplasia (OMIM

100800), metaphysal flaring of the humerus is not.[16] Chondrodysplasia punctata (OMIM 215100) is a radiological diagnosis characterized by punctate or stippled calcifications in epiphyseal cartilage and seen in peroxisomal disorders such as Zellweger syndrome (OMIM 614872), neonatal adrenoleukodystrophy (OMIM 601539), and infantile Refsum disease (OMIM 266500).[17]

As is now evident there are several orthopaedic aspects of SAMS syndrome. The highlighted aspects are those that are common within the four patients currently diagnosed with SAMS syndrome, but very rare to the outside population. The lumbar hyperlordosis, short ulnae, narrow sacosciatic notches and proximal femoral defects are more common and aspecific in the diagnosis of SAMS syndrome. Therefore, there is no further elaboration on these features in this paper. The bilateral clubfeet are a common finding in SAMS, however bilateral clubfeet are frequently found in children with and without syndromal disease, recognition and treatment is well-known worldwide, and therefore not further elaborated in this paper.

Conclusion

There are a number of striking orthopaedic diagnoses within the SAMS syndrome. In particular the scapulohumoral synostosis and the bilateral congenital ventral dislocation of the hips, are pathognomonic for the diagnosis SAMS syndrome. The differential diagnosis of the other orthopaedic aspects of SAMS syndrome is broad. Early diagnosis of each symptom allows for early recognition and subsequent follow-up. Treatment in most cases is conservative, although functional impairment can determine otherwise. Whenever a bilateral congenital ventral dislocation of the hips and or a scapulohumoral synostosis is

found or clinically suspected, SAMS syndrome should be considered as primary diagnosis until proven otherwise. This very rare autosomal recessive and clinically recognizable condition can be confirmed by GSC mutations.

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Figure legends

Figure 1. Patient B. Radiograph of the right foot. Persistent deformation after talectomy in the past.

Figure 2. Patient B. Anteroposterior pelvis roentgen image. Both hips are ventrally dislocated, and internally rotated. The articulating surface is between the greater trochanters and the inferior iliac bones.

Figure 3. Clinical features of patient B at the age of 19 years old.

Figure 4. Patient D. AP radiograph of both shoulders aged 2 years demonstrating bilateral scapulohumeral synostosis.

Figure 5. Patient D. AP pelvic radiograph aged 9 years. The pubic bodies, superior pubic rami and ischial bodies are absent. The upper femora have migrated into the pelvic cavity.

408 **Table 1.** Summary of orthopaedic aspects of SAMS syndrome.

Patient	A	B	C	D
Gender	Female	Female	Male	Male
Country of origin	Canada	Afhanistan	Pakistan	Bangladesh
Current age	28	21	8	3.5
Consanguinity (degree)	+ (first cousin)	+ (first cousin)	+ (first cousin)	+ (first cousin)
GSC nucleotide mutation	c.400C>T	chr14.hg19:g.95,204,793_95,511,597del	c.196_212del	c.355+1G>C
Predicted protein alteration	p.(Gln134*)	p.?	p.(Gly66Argfs*98)	p.?
Ventral dislocation of the hips	+	+	+	+
Scapulohumoral synostosis	+ (L+R)	+ (L+R)	+ (L)	+ (L+R)
Bilateral radial head dislocation	-	+	+	+
Delayed ossification of the pubic rami	+	+	+	+
Short humeri with distal metaphysal flaring	+	+	+	-
Lumbar hyperlordosis	+	+	-	-
Short ulnae	+	+	-	-

Narrow sacrosciatic notches	+	+	-	+
Proximal femoral defects	+	+	-	+
Bilateral clubfeet	-	+	+	+

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Figure 1

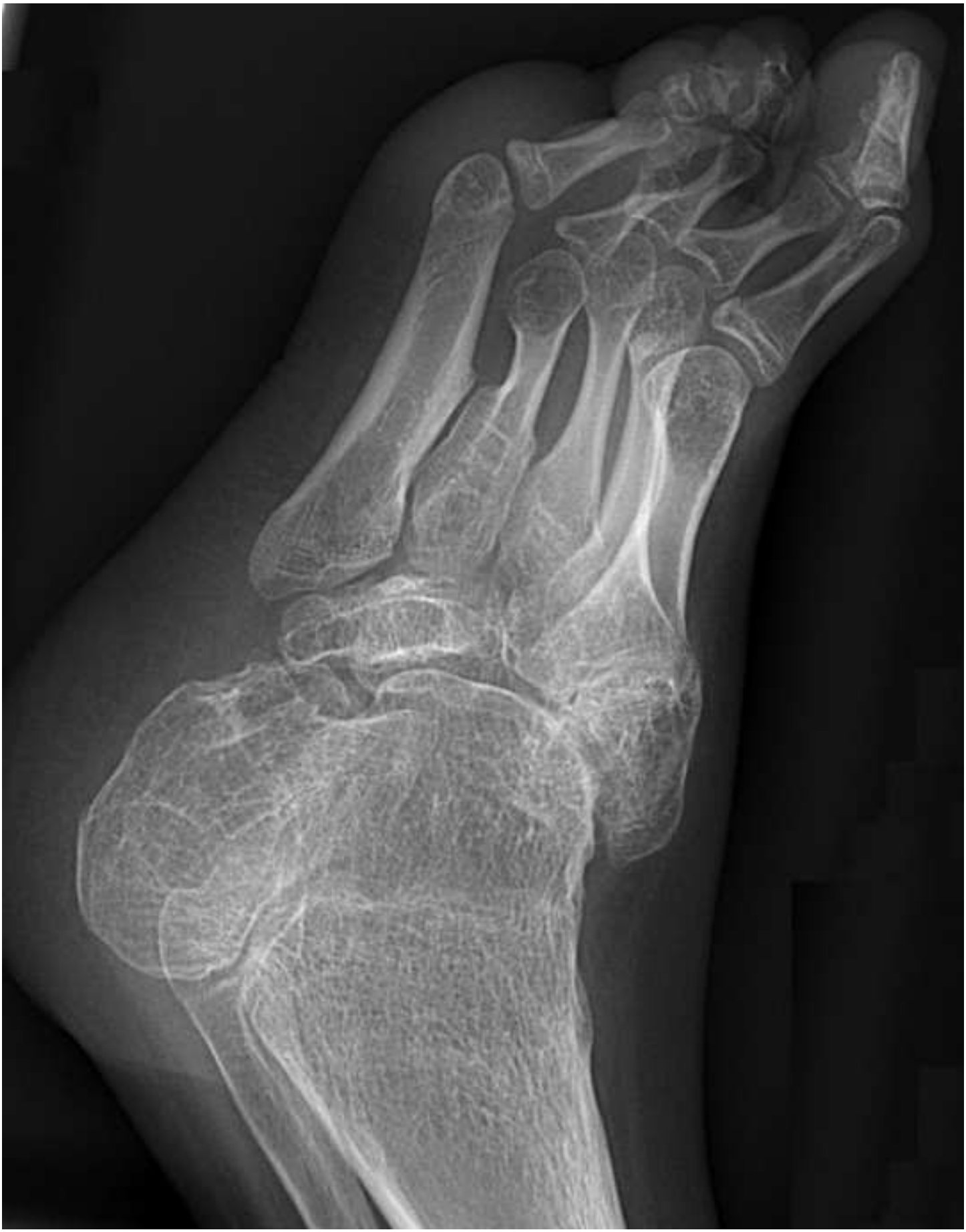
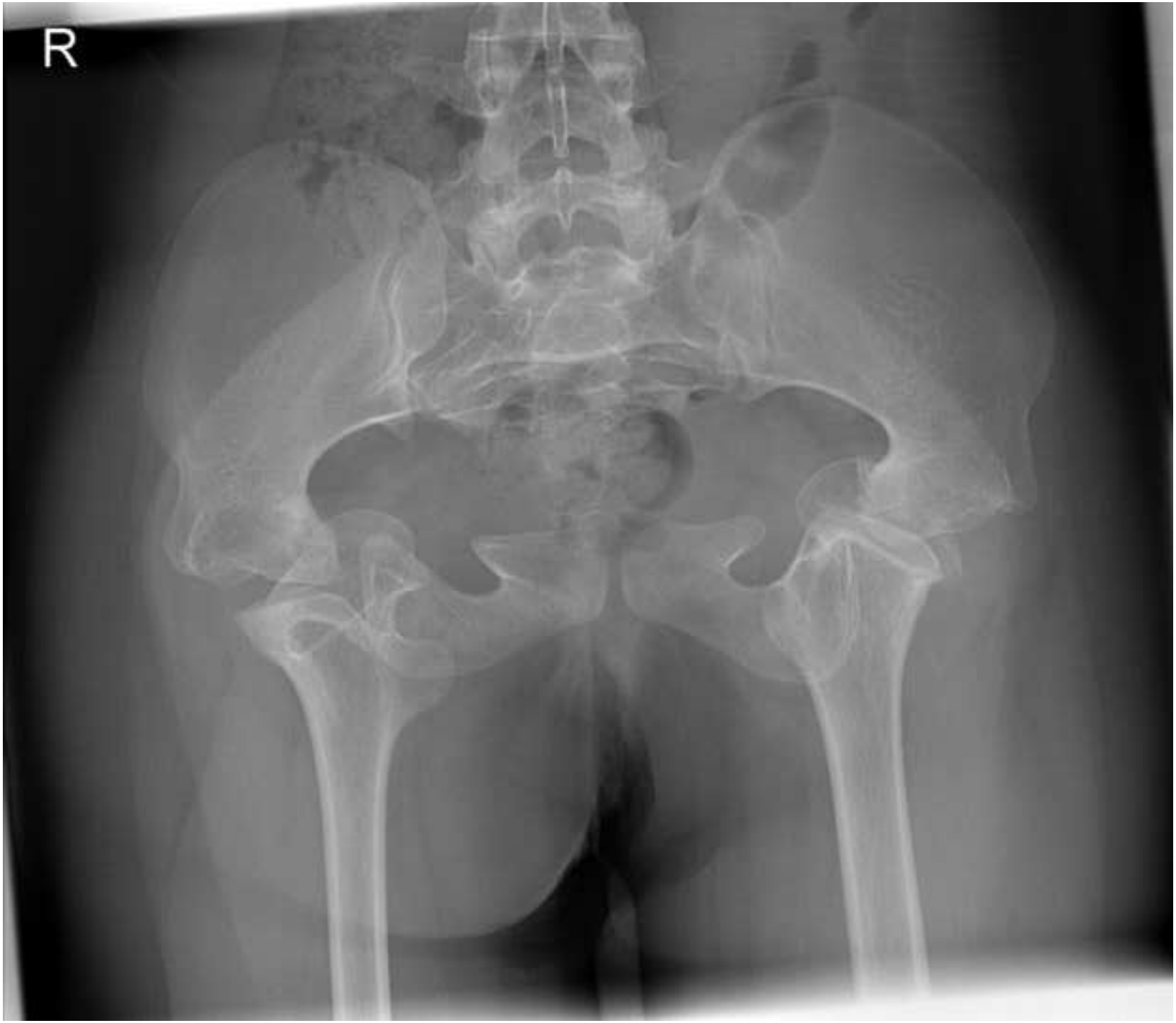


Figure 2



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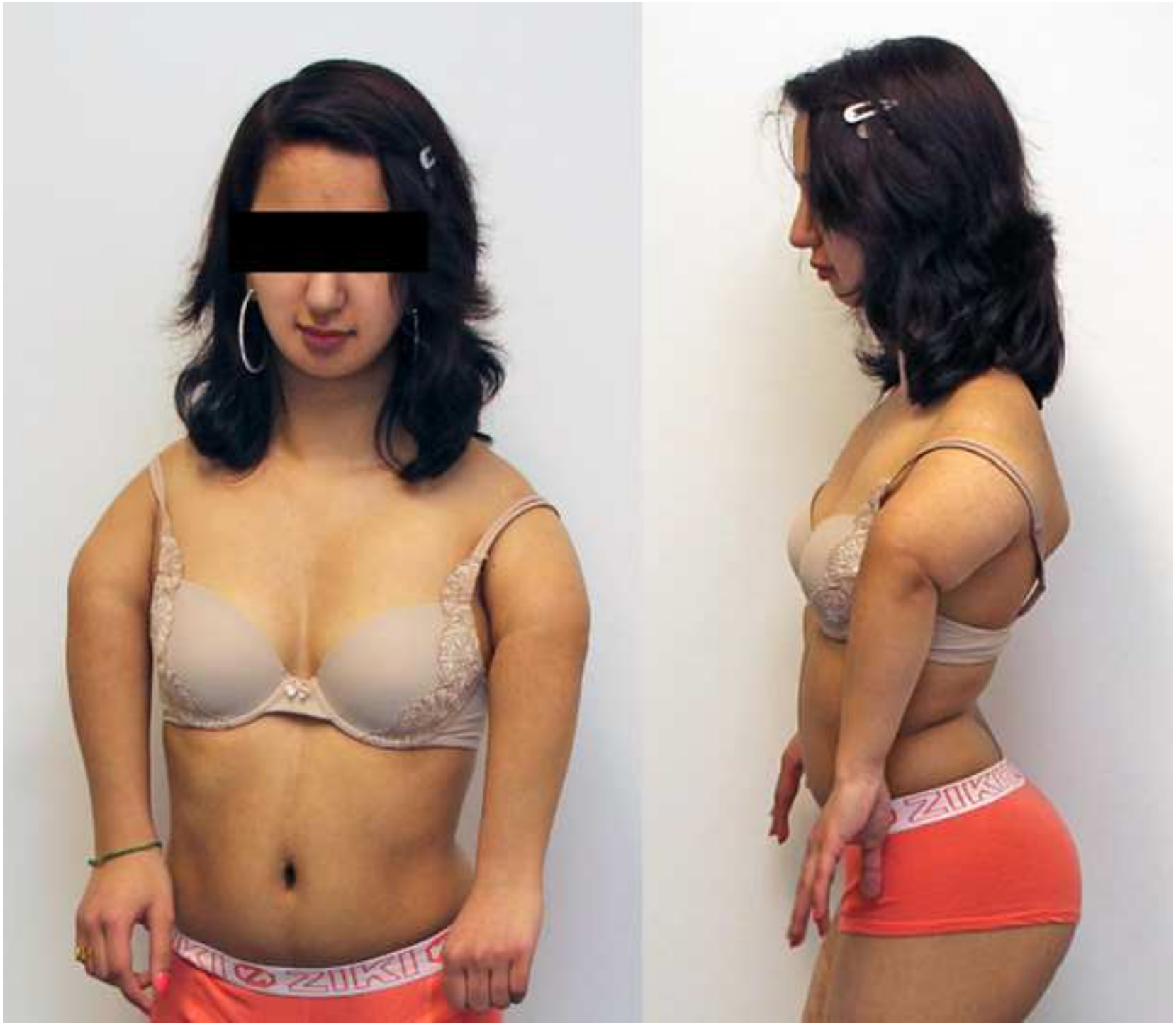

Figure 4

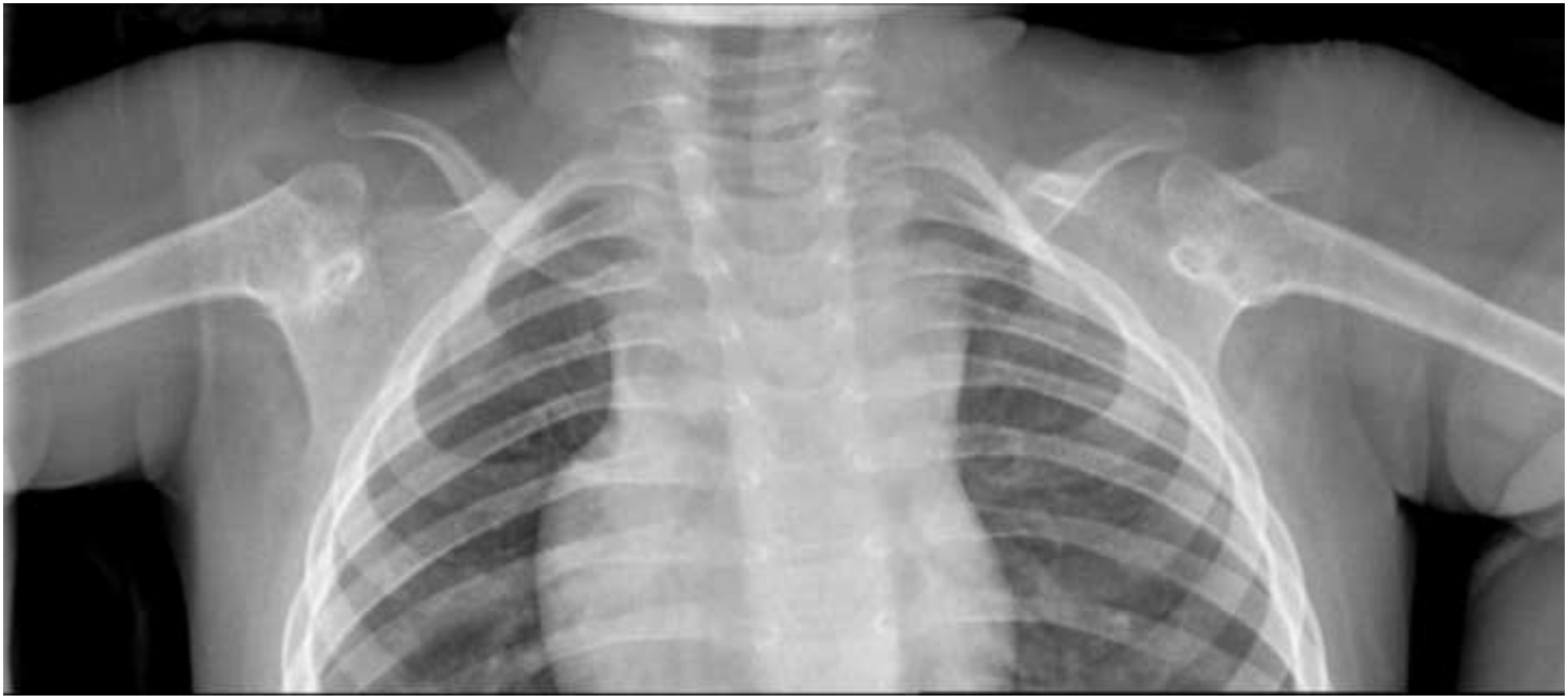

Figure 5