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Osteopetrosis Case Series from Tanzania

Lee Kapalisya Mwakalinga[1,2*], Rogers Joachim Temu[1,2], Honest Massawe[1,2], Mathias Ncheye[1,2], Zawadi Mahumbuga[1,2], Octavian Allexander Shirima[1,2], Mubashir Jusabani[1,2], Regnald Shoo[2], Anthony Japhet Pallangyo[1,2]

[1]Faculty of Medicine, Department of Orthopedic and Traumatology, Kilimanjaro Christian Medical University College, Moshi, Tanzania
[2]Department of Orthopedics and Traumatology, Kilimanjaro Christian Medical Center, Moshi, Tanzania
Email: *dr.wonglee@yahoo.com

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Abstract

Osteopetrosis is a rare group of sclerosing bone dysplasia characterized by diminished skeletal resorption. Typical osteopetrosis has the hallmark symptom of increased bone mass with related symptoms resulting from increased bone density. The mainstay of diagnosis is clinical and largely depends on the radiographic appearance of the skeleton. In our case series, three adults were studied, presented with history of recurrent fractures on the extremities sustained after low energy injuries, history of abnormal dentition and dental conditions, and phenotypic appearance of short stature, bossing skull, proptosis, and open fontanelles. From the clinical and radiographic presentations, a diagnosis of osteopetrosis as the underlying condition was reached. Two study subjects were managed conservatively, one was managed surgically following failed conservative management. In conclusion, conservative management is preferable and has good healing, even though there is no remodeling stage due to the abnormalities in osteoclast activities. If conservative management fails, surgical management is warranted.

Subject Areas

Microbiology

Keywords

Osteopetrosis, Conservative Management, Surgical Management, Tanzania

1. Introduction

Osteopetrosis is a rare group of sclerosing bone dysplasia characterized by diminished skeletal resorption [1]. It was first described by German radiologist Al-

bert Schonberg in 1904. Its hallmark feature of increase bone density as seen on radiography results from abnormality in osteoclast differentiation or function. It is variably referred to as marble bone disease or Albers-Schonberg disease [2]. Osteopetrosis comprises a clinically and genetically heterogeneous group of conditions. Traditionally, the disorder has been divided into two forms, the benign (adult, autosomal dominant) osteopetrosis variety that has autosomal dominant inheritance and present with relatively mild symptoms, and the malignant precocious (congenital, infantile, autosomal recessive) osteopetrosis that has autosomal recessive inheritance and present with severe early symptoms, those affected rarely survive beyond the first decade [3].

Typical osteopetrosis has the hallmark feature of increase bone mass with related symptoms and signs as a result of increase bone density. Macrocephaly, altered craniofacial morphology, altered modeling and remodeling system, encroachment of bone on bone marrow space and increase bone surface area that can lead to defect on bone marrow system and nervous systems [2]. Autosomal dominant osteopetrosis, was classified into type I and type II according to radiological appearance of the axial skeleton. Autosomal dominant type I is characterized by sclerosis of the skull mainly on the vault and is associated with calvarial thickening. Spine shows little sclerosis apart from the density of the vertebral arches. Autosomal dominant type II, sclerosis is mainly on the base of the skull, and presents with normal calvaria, thickening of vertebral end plates (sandwich-like or rugger jersey appearance) and presence of subcristal sclerosis of pelvic bone (convex arcs of sclerosis parallel to each iliac crest). Type II has high risk of fracture as compared to type I [3]. The mean number of fracture per patient has been reported as 4.4, predominantly involves the long bone [3]. Symptoms vary from fatal with autosomal recessive osteopetrosis to asymptomatic with autosomal dominant osteopetrosis.

Atypical osteopetrosis has typical features of increase bone sclerosis, and other systems are affected. Atypical symptoms vary in severity according to different mutation mechanism, gene and protein involved. Most Intermediate Recessive Osteopetrosis (IRO), type II carbonic anhydrase deficiency and other varieties are considered as atypical osteopetrosis. Type II carbonic anhydrase deficiency is associated with renal tubular acidosis and other symptoms like mental deficiency, hypotonia, apathy and muscular weakness which can be explained by metabolic acidosis [4].

Of recent, X-link inheritance pattern and intermediate recessive osteopetrosis has been classified to those affected to the degree between severe autosomal recessive osteopetrosis and mild autosomal dominant osteopetrosis. These patients with intermediate recessive osteopetrosis may present with short stature, anaemia, hepatomegaly and multiple fractures depending on severity of the defect [5].

Some literature classify as classic osteopetrosis, neuropathic osteopetrosis and autosomal recessive osteopetrosis (ARO) with renal tubular acidosis (RTA) [2]. Classification of the condition has been challenging as one disease has different

inheritance pattern, different mutation mechanism, gene and protein involved (Table 1).

Autosomal recessive osteopetrosis has estimated incidence of 1 in 250,000 births and autosomal dominant osteopetrosis has an incidence of 5 in 100,000 births. The overall incident is difficult to estimate as a single disease has many genes and different inheritance pattern [6]. Likewise, the presentation and severity of symptoms vary widely, ranging from neonatal onset with life threatening complication to the asymptomatic and those with typical symptoms and those with atypical symptoms. Current more than 10 genes variant have been identified as the cause of osteopetrosis [4] [6].

In this study, we present three cases of osteopetrosis. It was considered worth reporting these cases and discussing its clinical presentation, treatment options, outcomes and complications. The aim of describing these cases scenario is to help colleagues faced with similar cases.

2. Methodology

Prospective single centered Case series study was conducted at Kilimanjaro Christian Medical Center (KCMC) in the Department of Orthopedics. KCMC is Institution of the Good Samaritan Foundation of Tanzania located in Moshi Municipality, North-eastern Tanzania. The hospital has 650 bed capacity and is the second largest consultant zonal referral hospital in the country serving patients from northern and central regions of Tanzania. It is the teaching hospital for the Kilimanjaro Christian Medical University College, which offers undergraduate and post-graduate training.

Three cases were followed up for more than 5 years. All of them attended as outpatient and admitted several time in the course of their management. All of them had a history of recurrent trivial injury that led to fractures, and all of them were subjected to nonoperative treatment for most of their fractures. Two proximal femur fractures were operated on.

2.1. Case 1

A 36 years old male from Moshi, Kilimanjaro Northern Tanzania, presented with injury to both thighs, after being involved in a motor traffic crash. This happened after jumping off from a backward moving car at a low speed of about 20 km/hour. And landed on a standing stance, suddenly he experienced severe pain, unable to remain standing, and unable to move the lower limbs. He had history of recurrent bone fracture on the extremities; 2 times on tibia, 3 times on femur, once on radius/ulna and humerus. All fracture happened after trivial injuries, and were managed nonoperatively at our facility. Also, he has history of hearing loss for about 10 years which is not associated with ear pain, discharge or tinnitus. Currently, he is using hearing aids. He is a last born in the family of 6 children. One of his elder brothers has similar condition of recurrent bone fractures, short stature, poor dentition and boosing skull. The rest of the family members are phenotypically normal. The index has no history of alcohol use and

Table 1. Classification of osteopetrotic conditions, modified from the Nosology and Classification of Genetic Skeletal disorders (2006 revision).

Condition	Inheritance	Mutation mechanism	Gene	Protein
Osteopetrosis, severe neonatal or infantile forms	AR	Loss of function	*TCIRG*1	Subunit of V-ATPase pump
			RANKL	Receptor Activator for Nuclear Factor κB Ligand
			*OSTM*1	Osteopetrosis associated transmembrane protein
			*CLCN*7	Chloride channel
			RANK	Receptor Activator for Nuclear Factor κB
Osteopetrosis, intermediate form	AR	Loss of function	*CLCN*7	Chloride channel
			*PLEKHM*1	Pleckstrin homology domain containing family M, member 1
Osteopetrosis with renal tubular acidosis	AR	Loss of function	*CAII*	Carbonic anhydrase II
Osteopetrosis, late-onset form (Albers-Schönberg disease)	AD	Dominant negative	*CLCN*7	Chloride channel
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	XL	Loss of function	*IKBKG* (*NEMO*)	Inhibitor of kappa light polypeptide gene enhancer, kinase of
			Kindlin-3	Kindlin-3
Leukocyte adhesion deficiency syndrome (LAD-III) and osteopetrosis	AR	Loss of function	*CalDAG-GEF*1	Calcium and diacylglycerol-regulated guanine nucleotide exchange factor 1
Pyknodysostosis	AR	Loss of function	*CTSK*	Cathepsin K
Osteopoikilosis	AD	Loss of function	*LEMD*3	LEM domain-containing 3
Melorheostosis with osteopoikilosis	AD	Loss of function	*LEMD*3	LEM domain-containing 3
Dysosteosclerosis	AR			
Osteomesopyknosis	AD			
Osteopathia striata congenita with cranial stenosis	XL	Loss of function	*WTX*	Wilms tumour gene on the X chromosome
Osteosclerosis, Stanescu type	AD			

no history of cigarette smoking, not married. On examination; he was fully conscious, has hearing aids bilaterally, not pale, afebrile, breathing through open mouth. Vitals were stable, healing loss, anosmia, however he has good memory, no lateralizing signs and other cranial nerves were intact. Oral-Malocclusion, poor dentition arrangement and size, lost two teeth. Short stature (length—137 cm) BMI—29.8 Kg/m^2 (from personal record file). Head; bossing skull Pulsatile anterior fontanelle wide open, communicating sutures, frontal bossing with oc-

cipital-frontal circumference of 55 cm. Upper limbs; proportionally short, slightly bowed outward at elbow and spread fingers. Lower limbs; proportionally short, outward bowing femur and has short webbed toes. Slight swelling at proximal thigh bilaterally, both lower limbs were externally rotated, sensation were intact. We did skull, spine, pelvic and femur X-rays. Several abnormalities were noted on skull X-ray which shows abnormal open and communicating sutures, small sinuses and poor dentition, thickened base of the skull (**Figure 1**). On pelvic and femur X-rays, there are sclerotic and lucent bands, dense bones, marrow occlusion, and bones are club-like with coxa-valgus deformity, bilateral femoral subtrochanteric fractures, and several old healed fractures (**Figure 2**). Laboratory; complete blood picture parameters were within normal range, serum creatinine, urea and uric acid were within normal range. Liver function tests and blood minerals (calcium, phosphate) and electrolyte (sodium, potassium and chloride) were within normal range. However, free T4 were 42.3 ng/ml (reference 52 - 127 ng/ml), free T3 were 2.73 ng/ml (reference 0.69 - 2.15 ng/ml), TSH and PTH were within normal range. The underling medical condition was known to be Osteopetrosis, hence the diagnosis was pathological bilateral fracture of femur. The patient was managed by non-operatively with skin traction for 8 weeks, analgesic and physiotherapy. Light weight of 3 kg was applied as traction and bed foot was elevated to provide counter traction. Monitoring of the patient was done daily during word rounds and isometric muscle exercise was done daily by physiotherapy team. At 8-week since admission, control X-ray was done which shows some callus formation on both femurs (**Figure 3**) and clinically with signs of healing. Patient was taken off the bed with the aid of walking chair, ambulated for 2 days then discharge home with axillary crutch. Follow-up plan was made; after 1-month, weight bearing as tolerated but with axillary crutch for support, at 2 month full weight bearing without crutches and at 3 and 6 months control X-rays was done. Current patient resumes his activities with full range of motion at hip joint and about 100 - 110 degree knees flexion.

2.2. Case 2

A 50 years old female from Same Kilimanjaro is known with Pyknodysostosis (Osteopetrosis Acro-osteolytica). She had history of multiple fractures; three times on right femur, five times left femur, twice left tibia and several stress fractures in her lifetime. All fractures occur after trial injury, except the open fracture tibia/fibular which she sustained after being knocked by a moving motorcycle as a pedestrian 2 years ago. She has history of abnormal dental arrangement, dental pain and sustained iatrogenic fracture of mandible during tooth extraction which was fixed with tension wire band. She has recurrent chest symptoms cough and difficulty in breathing since her childhood. She is a teacher, married and they have 2 children who are normal phenotypically. She was born in the family of 8 members, her parent and 2 siblings are normal phenotypically, while the remaining four members has the same phenotype appearance with history of recurrent fracture and dental conditions. Her parents were first

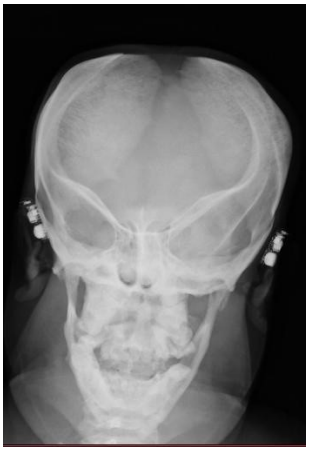

Figure 1. Skull X-ray (Case 1).

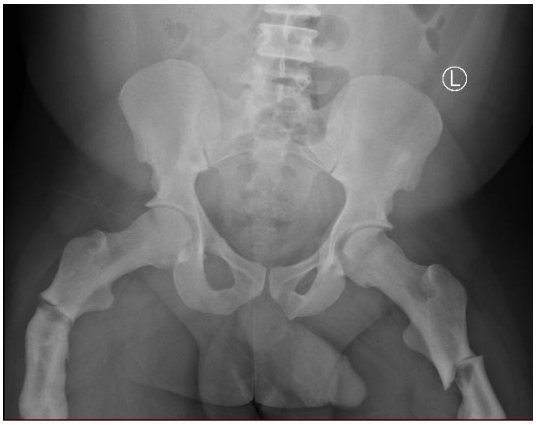

Figure 2. Pelvic and femur X-ray (Case 1).

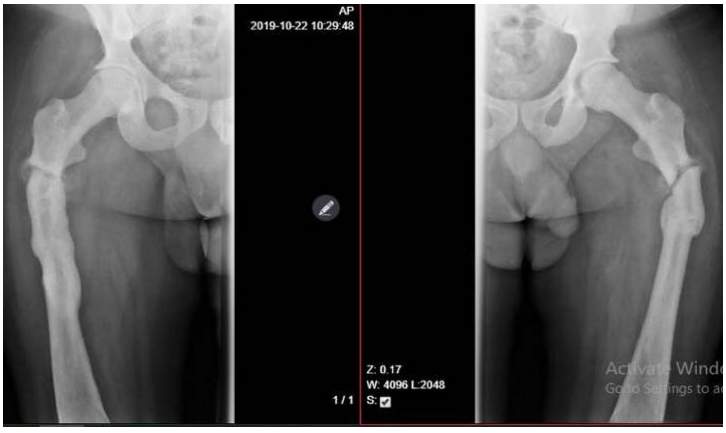

Figure 3. Control X-ray at 8 week since admission (Case 1).

cousin. On examination; she had short stature height about 125 cm upper limb and lower limbs are proportionally short, boosing skull, protruded eye ball, open fontanel, weight 45 kg, no mandibular angle, mandible fixed with tension wires band, abnormal dental arrangement. Fingers has increased crease on the dorsal surface. Blood workout was within normal parameter. Radiological work out;

pelvic and femur X-rays show sclerotic and lucent band, dense bone, marrow occlusion, healed fractures at multiple sites with poor remodeling of left femur and healed fractures with implants right femur (**Figure 4**). All other fractures were managed nonoperatively except subtrocantheric fracture left femur were ORIF with plate and screw was done 3 years ago. And for open fracture T/F, Surgical Debridement (SD) was done, fracture reduced and fixed with rush rod then above knee posterior slab cast was applied. Both surgeries was complicated with several difficulties including; longer operating time, increased resistance to reaming, drill bit breakage, difficulties in screw positioning, marrow perforation and introduction of rush rod. Stitches was removed in 2 weeks, wound healed by primary intention without infection. Circular cast was applied. Follow up was done in 6 weeks where cast was removed and Proximal Tibia Brace (PTB) was applied and patient was allowed to partial weight bear with the aid of elbow crutch. After 12 weeks, control X-ray was done and patient was allowed to full bear weight. A year letter, a patient came complaining of spontaneous pain and deformity on the same leg, follow up X-ray left tibia/fibular (T/F) shows non-union with implant failure (**Figure 5**). We managed to remove the proximal part of the implant, and then refreshen fracture margin, insert bone graft in-between the fracture ends and oblique osteotomy of the fibular was done to allow weight transfer to tibia (**Figure 6**). PTB was kept and patient was allowed to partial bear weight with the aid of axillary crutch. Patient was followed up at clinic, at 6 week, 12 week and current the patient can full bear weight.

2.3. Case 3

A 41 years old female, comes with history of injury to her right thigh sustained after fall from standing height, there was history of pain and unable to use the limb. She has been attending at our center since her childhood due to recurrent history of fractures of the extremities related to trivial injuries. Ten times tibia/fibular fractures, three times left femur fractures, three times right proximal femur fractures and 2 times right radius and ulna fractures. Also has history of recurrent pus discharge from her chin, she was diagnosed with osteomyelitis of the mandible and was operated six times due to the same. She is fourth born in the family of 11 members, and she is the only one with the condition, she is not married and has no child. She is peasant, standard 5 drop out school due to the current medical condition. On examination she has boosing skull, protruded eye balls, no mandible angle, surgical scar on the left chin that healed by secondary intention and short stature of about 134 cm. Right forearm deformed proximally with posterior angulation. Lower limb; left is shorter by 5 cm and with angular malformation. Blood work up; full blood picture and serum calcium were within normal range. Plain spine X-ray shows dense lumber vertebral and alternating sclerotic band at vertebral ends (**Figure 7**), pelvic and femur X-ray pre-operation shows sclerotic and lucent bands, dense bone, marrow occlusion and bone are club like with coxa-valgus deformity, right proximal femur transverse fracture and several old healed fractures (**Figure 8**). All fractures of tibia/fibular and

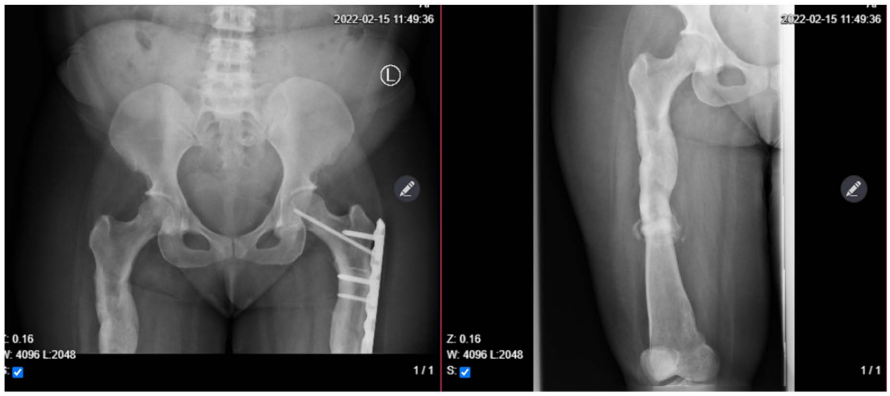

Figure 4. Pelvic and femur X-ray (Case 2).

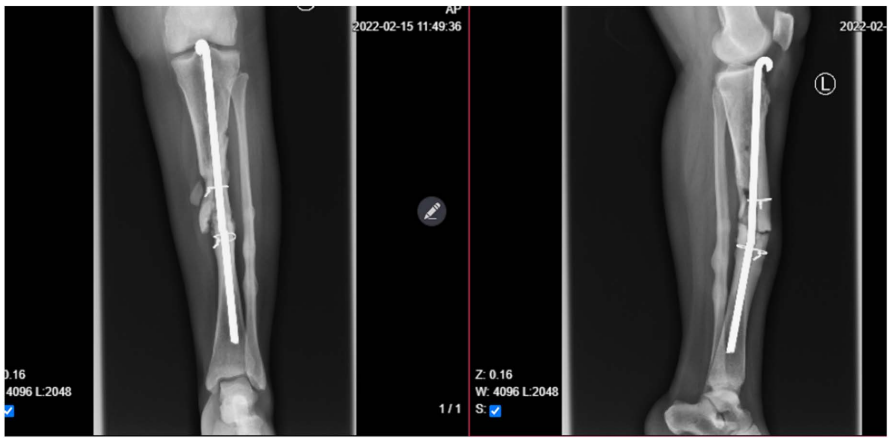

Figure 5. X-ray left tibia/fibular (Case 2).

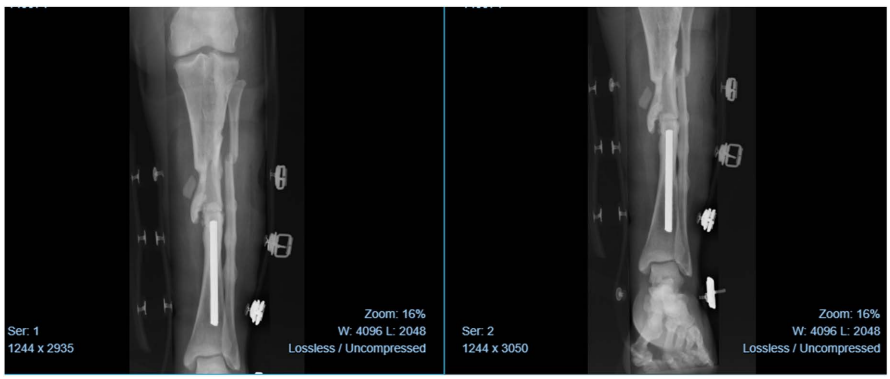

Figure 6. X-ray left tibia/fibular with bone graft (Case 2).

radius/ulna was managed conservative management and healed without any other complication apart from angular deformities and poor remodelling. For the fracture of femurs; left femur, the first two were managed conservative management and for the third fracture non-operative management failed after traction for 12 weeks. Then surgical intervention was warranted, where fracture site was opened, margin refreshed and rush rod was applied. The surgery was complicated by difficult perforating into the marrow, break of one drill

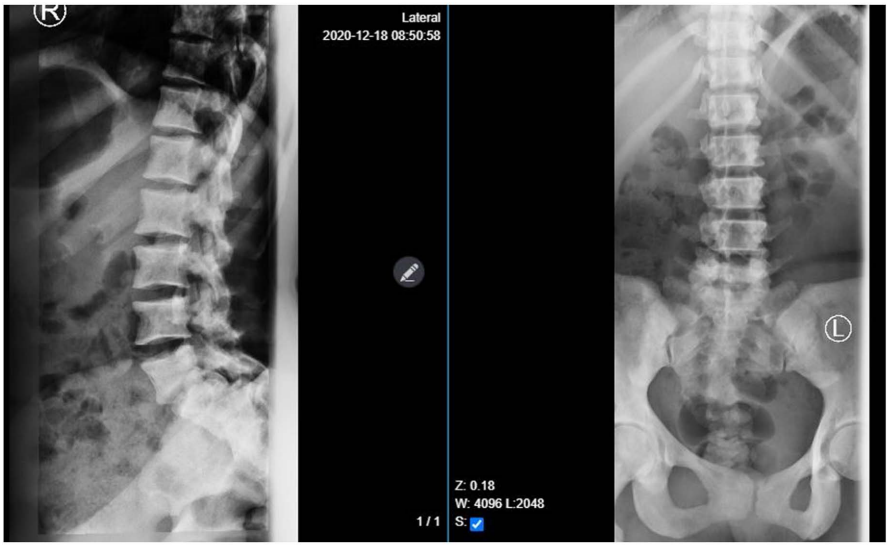

Figure 7. Spine X-ray (Case 3).

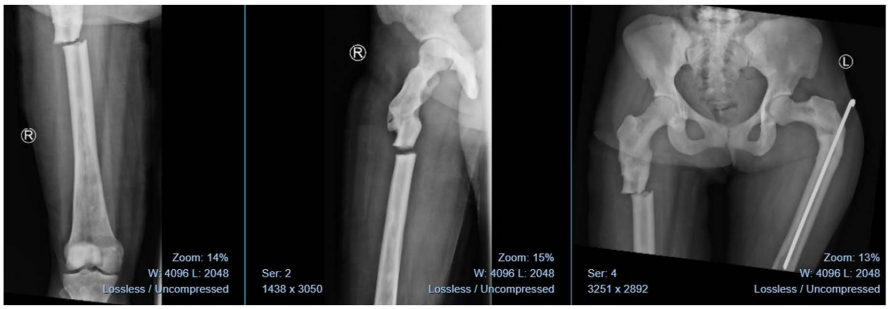

Figure 8. Pelvic and femur X-ray (Case 3).

bit and long operating time. For the right femur, the first two fractures were managed non operatively, third fracture, patient requested to be managed surgically, her concern was deformity and she has bad experience with previous left femur fracture which she stayed on traction for 12 weeks. Then she was operated on right femur, where lateral approach for proximal femur followed, fracture site opened, cleaned and retrograde perforation for the entry point was done using multiple new drill bit, fracture reduced and in antegrade, rush rod was inserted. After operation the patient was kept on HKAFO. Long operating time and difficult perforating into the marrow was encountered. Postoperation X-rays show rush rod in situ and well-reduced fracture (**Figure 9**). Follow up plan was scheduled to attend at orthopedic and dental clinics. At 6th week, she was allowed to partial weight bear with the aid of axillary crutch. At 12th week, HKAFO was removed and allowed to weight bear as tolerated with the aid elbow crutch on the contralateral side. Recent she has been complaining of acute history of low back pain without radiculopathy symptoms and no history of trauma. Lumbar CT scan was done and reviled normal spinal canal and neuroforamen diameter. However, pars-intercularis fracture on right side at L4/L5 was noted (**Figure 10**).

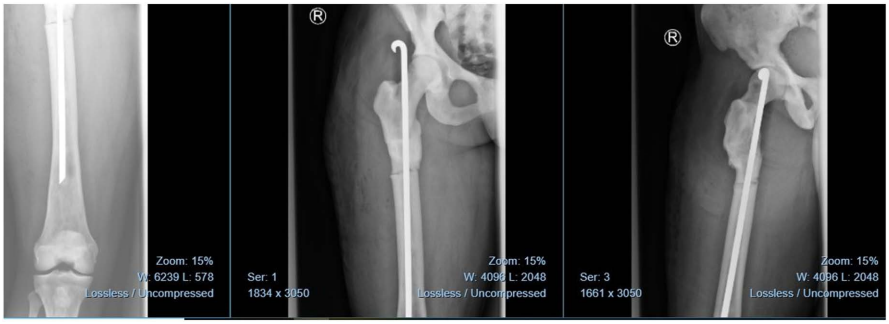

Figure 9. Post operation X-ray (Case 3).

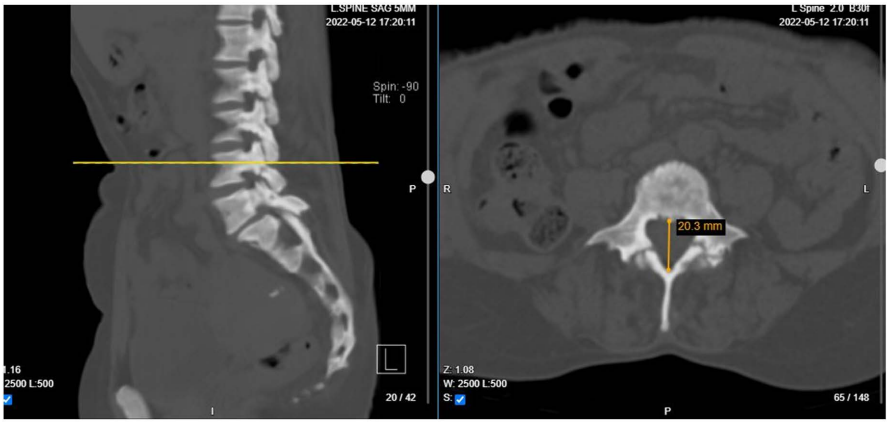

Figure 10. Lumbar CT scan (Case 3).

3. Discussion

Mainstay of diagnosis is clinically and largely depends on radiographic appearance of the skeleton as noted in our cases. Typical radiological feature comprises: bone in bone appearance especially in vertebrae and phalanges, focal sclerosis of the base of the skull, pelvis and vertebrae end plates (sandwich vertebrae/rugger jersey vertebrae), bone modelling defects at the metaphysis of long bones such as funny-like appearance (Erlenmeyer flask deformity) and diffuse sclerosis on the spine, skull, pelvis and appendicular bones. All of the cases presented have typical features, even though there are some variation in presentation and severity as can be explained by number of fractures. Additional symptoms can help to distinguish between subtypes of the condition, assess severity of the condition and its mechanical compression effect [1] [2].

Plan radiography and computed tomography (CT) are the most useful modalities to evaluate osteopetrosis. Magnetic resonance imaging (MRI) and/or CT can be used to evaluate the amount of remaining bone marrow space, to evaluate for narrowed neuroforamina, neurocranium, hydrocephalus, and brain abnormalities in neuronopathic form of osteopetrosis. In our third case, lumbar CT scan was done as the patient has acute history of low back without radiculopathy symptoms, which was not related to trauma, however we found pars-intercularis fracture right side at L4/L5 (**Figure 10**). Abdomen ultrasonography can be used to evaluate for hepatosplenomegaly [5].

Genetic testing can be used to confirm diagnosis, help for genetic counselling and differentiate subtypes as they have variable response to treatment and prognosis [7], however to none of our patient genetic testing was done due to in-availability of the test in our setting. Bone biopsy can distinguish between osteoclast-poor and osteoclast-rich subtypes of ARO, but this is invasive and rarely performed. Blood work up; Full Blood cells count, can be used to evaluate leukocytosis or leukocytopenia, thrombocytopenia, and anemia with low reticulocyte count. Calcium concentrations in blood and urine can be used to evaluate hypocalcemia and secondary hyperparathyroidism [2]. Our cases have normal blood work up, with slightly reduced free T4 and elevated free T3 was noted in first case.

Other workup; Ophthalmologic examination including Visual Evoked Potential (VEP) to evaluate for optic nerve atrophy, otorhinolaryngologic examination to evaluate for choanal stenosis, Electroencephalography (EEG) to detect pathologic changes associated with neurodegeneration and neurologic examination to evaluate development [7] [8].

No effective medical treatment for osteopetrosis exists. Treatment is supportive and team approach according to the presents symptoms and complication. Fractures are managed conservatively with non-operative treatment. However, once conservatively management fails; surgical management is warranted [9]. Some literatures reported non operative management to associates with delayed or nonunion, and subsequent coxavuras deformity [10]. For our cases, the first case we had good outcome with non-operative and all the fractures healed well, however without remodeling and some deformities on the extremities, current he has resumes his daily activities. Second and third cases several fracture was managed non-operatively and operatively for proximal femur fracture and open fracture tibia/fibular. Srivastay *et al.* suggested operative management for intertrocanteric and subtrocantheric femur fractures due to several risk; including increase length of hospital stay, angular deformity, nonunion and delay consolidation [11]. In our follow-up for the third case implants pullout and coxavuras deformity was noted on left femur, despite those complication patient opted for operative intervention on her recent fracture right proximal femur. Her operation took 4 hours and we had to use multiple drill bit to open the bone marrow.

Operative Intervention has high rate of intraoperative and post-operative complication. The complications are due to abnormal bone strength and fragility, occluded marrow and nutrient blood vessels. Some of the complication most surgeon encountered are increased resistance to reaming and screw positioning , longer operating time, high risk of iatrogenic fracture, drill breakage, overheat of the bone and drill bits and high rate of infection, peri-prosthetic fracture and re-fracture through screw holes after removal of the implants [10] [12]. Some of these difficulties were encountered to our second and third cases.

Other symptoms like hypocalcaemic seizure are treated with calcium and vitamin D supplementation. And for those with bone marrow failure, are treated with red blood cell and platelets transfusion. Hematopoietic stem cells trans-

plantation (HSCT) is reserved for severe form of ARO (2).

4. Conclusion

Thus, in our facility, conservative management is preferable, and has good healing however there is no remodeling stage due to the abnormalities in osteoclast activities. Our current challenge is the inability to perform genetic testing that would have help to explain the differences in clinical presentation, hence identify new therapeutic approaches.

Author's Contributions

All authors read and approved the final manuscript for publication.

Patient Consent

Informed consent was obtained from all patients.

Conflicts of Interest

Authors declare no competing interests.

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