Case Report

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OSTEOPETROSIS WITH MAXILLARY OSTEOMYELITIS: REVIEW OF LITERATURE AND CASE PRESENTATION

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ABSTRACT:

Osteopetrosis (OP) is a defect in normal bone remodelling process, due to disturbance in function of the osteoclasts, those defective or immature cells occur as a result of genetic defect in more than 10 genes. OP is inherited as autosomal recessive or dominant, the autosomal recessive is fatal shortly after birth, while the dominant type has normal life expectancy, and there is an intermediate form between the two forms. Patients affected by the autosomal dominant variant discovered incidentally at late childhood, they may presented with complications such as fractures to minor trauma or osteomyelitis of the jaws mainly that of the mandible, while that of maxilla is rare. The aim of this report to present a case of maxillary osteomyelitis associated with OP (late onset) and to review the literature regarding this context.

Key words: Osteopetrosis, Marble bone disease, Osteomyelitis.

INTRODUCTION:

Normal bone remodelling is a balance between osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells), any defect in this equilibrium will result in increased or decreased bone density, causing to a pathologic conditions. Increased bone density conditions are hereditary defects affecting the osteoclasts resulting in bone overgrowth, leading to abnormally dense but weak bone susceptible to fractures.[1-6] One example of these conditions is osteopetrosis(OP) which is caused by poorly differentiated or dysfunctional osteoclasts with mutations affecting at least 10 genes.[2]

OP or marble bone disease is inherited as autosomal recessive(AR) and autosomal dominant(AD),[3-5,7] the latter is also named Albers-Schonberg disease has an incidence of 1 in 20.000 births while the autosomal recessive has an incidence of 1 in 250.000 births.[2,8]

Although OP is broadly classified into Autosomal recessive OP(ARO), intermediate form and autosomal dominant OP(ADO) (type I and II).[1,2,4,5,9,10] OP encompasses a group of highly heterogeneous conditions, ranging in severity from asymptomatic to fatal in infancy. Intermediate autosomal

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recessive form is milder than malignant condition with significantly lower occurrence rate and may be discovered by chance during radiographic examination. The onset of the intermediate form at childhood and may presented with skeletal, haematological and/or neurological manifestations.[2,6,10] The infantile malignant autosomal recessive forms are fatal shortly after birth if not treated properly.[1-5,10] Despite the proper management they still have poor prognosis while the autosomal dominant form has good prognosis and may be discovered incidentally,[1-3,5] about 40% - 50% of ADO are asymptomatic[1-3,10] the rest may present with neurological symptoms such as pain, blindness, deafness, and facial paralysis because of narrowing of skull foramina due to failure of bone remodelling by the defective osteoclasts leading to nerve compression. ADO may also be presented with recurrent fractures to minor trauma or bone infection commonly osteomyelitis of mandible.[1,10] Osteomyelitis is induced by caries in 10% of patients due to reduced blood supply and obliteration of marrow spaces in osteopetrotic patients.[5,6,9] In spite of decreased vascularity of jaws in OP, still the maxilla better than the mandible in terms of blood supply and cortical bone morphology, for this the infection of the maxilla is rare in cases of OP compared to that of mandible.[8] The aim of this report was to present a case of maxillary osteomyelitis associated with OP and reviewing the literature on this context.

CASE DETAIL:

A 36 Years old male Libyan patient presented to Oral and Maxillofacial Surgery Department at Dental School-Benghazi University-Benghazi-Libya complaining of pus discharge from right posterior area of upper jaw and from infra orbital area. Past dental history revealed history of dental extraction since one year which was difficult, then the patient developed discharge and oral discomfort few months post extraction.

The patient admitted to our hospital on intravenous Augmentin 1.2 g and Metronidazole 500 mg eight hourly. Past medical and surgical history showed that he had undergone surgical operations for fractured both lower limbs. In his family history there were two nephews with the same problem of recurrent fracture to minor trauma, one nephew is a 16 years old female and the other is 9 years male.

The patient gave history of perirectal bleeding which examined by general surgeon who advised colonoscopy which revealed internal haemorrhoids, and abdominal ultrasound scanning which showed mild splenomegaly. The other history was insignificant.

In general the patient and his nephews are apparently short stature (figure 1),

surgical scars are seen on the anterior aspect of his legs (figure 2) and on lateral aspect of upper part of thigh of his female nephew associated with sinus (figure 3). Right infraorbital area of the patient's face showed sinus with history of frequent discharge (figure 4). Intraorally the patient is completely edentulous with sinus at the upper right molar area associated with exposed bone and necrotic materials (figure 5). The female nephew has full dentition and protruded maxilla with normal surrounding soft and hard tissues (figure 6) while the male nephew has frontal bossing and a partially edentulous maxilla with decayed teeth (figure 7).

Haemoglobin is obviously low (5.4 gm./dl.), red blood cells are 2.9 x 10^6 mm^3, haematocrit is 18.9%, MCV is 65.2 fl, MCH is 18.6 pg and serum phosphorus and alkaline phosphatase are with normal range, Serum calcium is minimally decreased (7.9 mg./dl.), erythrocyte sedimentation rate (ESR 19 mm/hr.) is slightly raised. Thyroid and parathyroid function tests are within normal range, bleeding profile including PT, APTT and INR are normal.

CT scan and posterio-anterior skull view of the patient showed increased bone density especially at the skull base, zygoma, and maxilla with obliteration of paranasal sinues (figure 8). On the right side of the maxillary bone, CT scan showed areas of bone irregularities may indicate the bone seqestra (figure 8). Orthopantomogram exhibited increased bone mass with impacted molars at each side of both jaws (figure 9). Views of the patient's lower limbs show plated fracture of both femurs and both tibias (figure 10). Radiographs of the male nephews revealed casted fractured tibia and healed fractured femur (figure 11), while that of female one showed plated fractured femur (figure12).

Form the history, clinical and radiological assessment, diagnosis of OP (late onset) was made.

Haematologist diagnosed the patient to have microcytic hypochromic anaemia and decided to start blood transfusion. After management haemoglobin become 12 mg/dl, RBCs of 5.3 x 10^6 mm^3 , haematocrit 39.4%, MCV 74.3 fl, MCH 22.6 pg. So that anaesthetist accept the patient for operation, under aseptic condition, necrotic bone exposed and because no mobile bone pieces found, saucerization performed but unfortunately no bleeding points reached (figure 13), wound closed and after three days of intravenous antibiotics the patient discharged, on follow up visits there was no improvement nor worsening of the case, we advised him to have hyperbaric oxygen, but unfortunately we lost the contact with him after that.

DISCUSSION:

Op ('osteo' means bone and 'petros' means stone) is a descriptive term that

refers to a group of rare, heritable disorders of the skeleton characterised by increased bone density on the radiographs.[2,7,8] It also named marble bone disease, Albers-Schonberg disease,[1,2,4-6,9] osteopetrosis generalisata,[1,9] generalized congenital osteosclerosis, ivory bones, osteosclerosis fragilis generalisata.[7,8]

Epidemiologically the overall incidence of the OP is difficult to estimate, but 1 in 250.000 births account for autosomal recessive variant,[2,8] while 1 in 20.000 births for autosomal dominant type.[2] ADO or Albers-Schonberg disease which is the most common type of osteopetrosis is considered mild or benign form.[2]

Diagnosis of OP depends mainly on clinical features and radio-graphical examination, and these findings are sufficiently enough to make accurate diagnosis.[1,2,6] Gene testing is unnecessary especially in ADO[6,8] and restricted to confirm and differentiate between different types of increased bone density conditions, and it may help in estimating the prognosis, treatment response and recurrence risks. In confusing cases, high levels of creatine kinase BB isoenzyme and tartrate resistant acid phosphatase (TRAP) help in diagnosing ADO.[2,6,10] Bone biopsy is rarely performed as it is invasive but it can be used to differentiate between osteoclast-poor and osteoclast-rich variants of ARO.[2].Elevated serum alkaline phosphatase, low serum phosphorus and decreased serum calcium have been reported in cases of OP.[1] The present case was diagnosed depending on the clinical findings and the radiographical examination. Those finding along with the low serum calcium and anaemia were enough to reach the diagnosis.

Clinical features of this condition vary according to type of OP, ARO is fatal shortly after birth while ADO is asymptomatic and discovered incidentally on radiographs, but in late childhood or adolescence, patients with ADO may suffer pathologic fractures or osteomyelitis typically of the mandible.[1,2,9]

In general OP patients have short stature due to impaired longitudinal bone growth, and may presented with bone pain, recurrent fractures, hypocalcaemia, long bone bowing, hip and knee degenerative arthritis, osteomyelitis[1,4-10] and tetanic seizures, compressive neuropathies,[1,4,6-8,10] coxa vora,[5,7] macrocephaly, frontal bossing, hydrocephalus, hepatosplenomegaly[2,3,6,10] and pancytopenia rendering them susceptible to frequent bleeding, and recurrent infections leading to death.[2,10]

Some reports mentioned that patients with OP may suffer ostesosarcomas.[5,7].Bedi el al.[9]

mentioned that OP is associated with increased susceptibility to respiratory tract infections, and cardiac problems. Visual disturbances other than blindness such as hypertelorism, strabismus and nystagmus have been reported,[6,10] from photos of our patient it is obvious that he has strabismus (left convergence squint).

Dental anomalies in ARO include delayed eruption, congenitally missing teeth, malformed root and crowns, poor tooth calcification and dental caries.[1-10]

The other variants of OP complicated by neurodegeneration, and involvement of skin (anhidrotic ectodermal dysplasia and lymphedema), renal (renal tubular acidosis) and immune systems (immunodeficiency and overwhelming infections).[2]

Recurrent infection (maxillary osteomyelitis), frontal bossing, left convergence squint, missed teeth, short stature, recurrent fractures, anaemia, and splenomegaly were positive finding in our patient consistent with most of reports in literature.

Radiographs of osteopetrotic patient showing diffuse sclerosis (chalky white)[1-3,5], 'bone in bone' appearance especially in phalanges[1,2,5,7,8], funnel-like appearance (Erlenmeyer flask deformity) which is due to defective metaphyseal bone remodelling of long bone and 'sandwich' verteberae and 'rugger-jersey' spine[2,5,7,9]. Spondylosis of lumbar spine has been reported[5,7].

The paranasal sinuses and mastoid air cells are underpneumatised in radiograph of patients with OP.[5,9]

Hypercementosis and increased thickness of lamina dura are seen in radiograph of OP patients.[1,7] Constriction of canals housing neurovascular bundles that supply teeth and jaws, along with obliteration of marrow spaces and pulp chambers are also seen on the radio-graph of osteopetrotic patients.[4-6,9] The radiograph of the present case showed diffuse sclerosis (absent corticocancellous demarcation), obliteration of paranasal sinuses, and clear but narrow mandibular canal and also showed remaining roots and impacted wisdom teeth which looked poorly mineralized.

ADO has two types on the radiograph, Type I characterised by massive sclerosis of skull, and thickening of skull vault while Type II is distinguished by sclerosis of the skull, mostly at the its base and also shows thick dense upper and lower borders of the vertebrae end-plates with normal appearance in the middle giving a 'Rugger-Jersey spine'[1]

In review of literature, the family history found to be variable, most of reported cases showed insignificant family history,[1,3-9] while others mentioned few cases of OP born of

consanguineous marriages.[3] Unlike the previous reports, the present case showed significant family history where two nephews were affected.

Etiologically the OP occur due to mutation of at least 10 genes causing defects in maturation of stem cell into osteoclast.[2] The abnormalities may also involve osteoclast microenvironment , osteoblast precursor cells or bone matrix, the other possible causes of defects of osteoclast include synthesis of abnormal parathyroid hormone, defective production of interleukin-2 (IL-2) or superoxide.[10] So dysfunctional or immature bone resorbing cells resulted, leading to dense and brittle bone due to abnormal remodelling.[1,2,8] Increased bone density with absent or defective compensating resorption lead to narrowing of skull foramina causing neural compression with symptoms like neuralgias, blindness and deafness. This uncontrolled bone deposition with absent or defective marrow space result in pancytopenia which in turn stimulate the extra-medullary haematopoiesis with hepatosplenomegaly and hypersplenism which further worsen the pancytopenia.[1-4,10] Obliteration or narrowing of the neurovascular canals and marrow spaces result in decreased blood flow and pancytopenia which in-turn lead to increased susceptibility to infections namely osteomyelitis[9] which is also affected by limited antibiotic availability at the affected site.[6]

The Nosology Group of the International Skeletal Dysplasia Society classify OP and other increases bone density conditions into several distinct entities based on clinical features, mode of inheritance and underlying molecular and pathogenic mechanisms. Accordingly the OP includes sever neonatal or infantile form (inheritance: AR, defected Genes: TCIRG1, CLCN7, OSTM1,RANKL, and RANK), intermediate form (inheritance: AR, defected Genes: CLCN7 and PLEKHM1), late-onset form (inheritance: AD, defected Genes: CLCN7), OP with renal tubular acidosis (RTA) (inheritance: AR, defected Genes: CAII 'carbonic anhydrase II'), OP with ectodermal dysplasia and immune defect 'OLEDAID' (inheritance: XL, defected Genes: IKBKG'NEMO') and Leukocyte adhesion deficiency syndrome 'LADIII' and OP (inheritance: AR, defected Genes: kindling-3). Other increased bone density conditions comprises Pycnodysostosis (inheritance: AR, defected Genes: CTSK), Osteopoikilosis (inheritance: AD, defected Genes: LEMD3), Melorheostosis withosteopoikilosis (inheritance: AD, defected Genes: LEMD3), Dysosteosclerosis (inheritance: AR), Osteomesopyknosis (inheritance: AD), Osteopathia striata congenital with cranial stenosis(inheritance: XL, defected Genes: WTX) and Osteosclerosis, Stanescu type (inheritance: AD). ARO is further classified into classic, neuropathic and ARO with RTA.[2]

As the OP is considered primary sclerosis, it should be differentiated from sclerosis secondary to other pathological conditions. Secondary sclerosis may be seen in fluoride, beryllium, and bismuth poisoning, myelofibrosis, sickle cell disease Paget's disease (sclerosing form), hypervitaminosis D, hypothyroidism and malignancies such as lymphomas, leukaemia and osteoblastic metastasis such as breast and prostate cancer.[2,4]

Treatment of marble bone disease is symptomatic,[1-3,5] which include treatment of fractures and arthritis in specialised place, calcium and vitamin D for hypocalcaemia and tetany, red blood cell and platelet transfusions to compensate bone marrow failure. Surgical5 decompression to prevent serious complications such as blindness may be indicated, and also surgical and medical management of oral and dental problem is important particularly osteomyelitis. Calcitriol, steroids, calcium restriction, parathyroid hormones, erythropoietin, and interferon have been attempted to stimulate host osteoclasts.[1-3,6,7,9]

Osteomyelitis require high doses of proper antibiotics, surgical debridement and hyperbaric oxygen.[1,6,8] Sequestrectomy and segmental resection and reconstruction are also reported,[7].Hyperbaric oxygen improves the condition because of bacteriostatic and bactericidal effect, furthermore it increases the vascular supply and oxygen perfusion to the ischemic areas in the osteomyelitis.[9]

In severe malignant forms the only hope of long term cure is haematopoietic stem cell transplantation(HSCT)[1-3,6,79,10] resulting in 73% 5 years disease-free survival in cases of HLA-identical donors. As a bridge to transplantation or in OP types that unlikely to respond to HSCT, interferon gamma 1b has been attempted to improve immune function, increase bone resorption, and increase in marrow spaces.[2]

Splenectomy may be useful in some patients.[3] The prosthetic rehabilitation was reported to fulfil the requirements of the patient after control of the disease.[8]

The treatment of our patient was focused on cure of osteomyelitis by use of intravenous antibiotics and debridement, but to be accepted in the operating theatre it was necessary to manage the anaemia. Our haematologist carefully dealt with the case to reach haemoglobin of 12 mg/dl. Hence there is no improvement after the surgical management; the patient was advised to undergo hyperbaric oxygen therapy.

The prognosis of severe infantile form is poor with short life expectancy, most dying early in life where as the dominant form has good prognosis with normal life expectancy.[2]

The preventive measures reducing the risk of OP complications comprises prompt formal neurological assessment including brain MRI and EEG, regular ophthalmological surveillance based on visual evoked potential to detect optic nerve involvement,[2] routine oral and dental health surveillance and maintenance of oral hygiene to prevent dental caries and its sequel.[2,9] fluoride application and 0.2 % chorhexidine formulations have been advocated to control oral complications of OP.[4,9]

CONCLUSION:

Patients suspected to have osteopetrosis should be referred to specialists, even benign form with simple extraction should be managed by experienced specialist to minimize the risk of developing complications particularly.

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FIGURES:

Figure 1: shows the patient's nephews who are obviously short stature

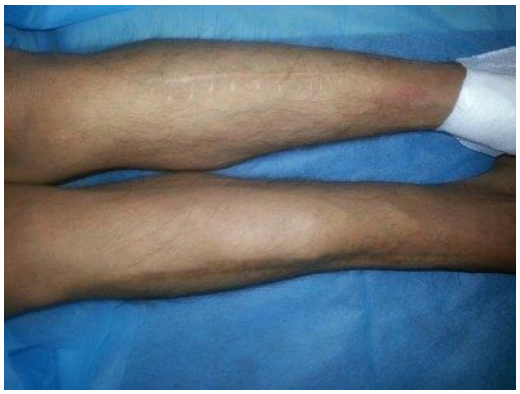

Figure 2: shows surgical scars of anterior aspects both legs.

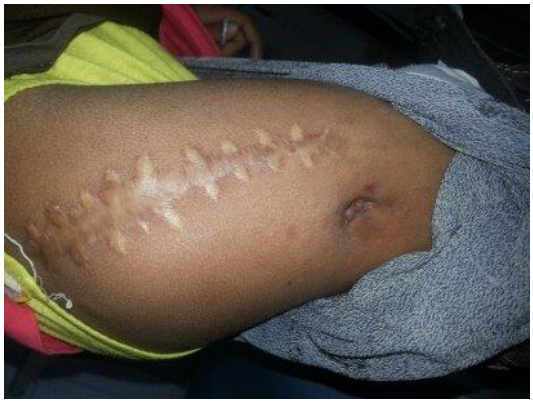

Figure 3: shows surgical scar and sinus on lateral aspect of thigh of the patient's female nephew.

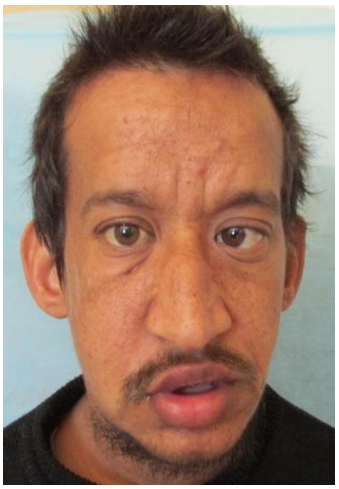

Figure 4: shows sinus at right infraorbital area.

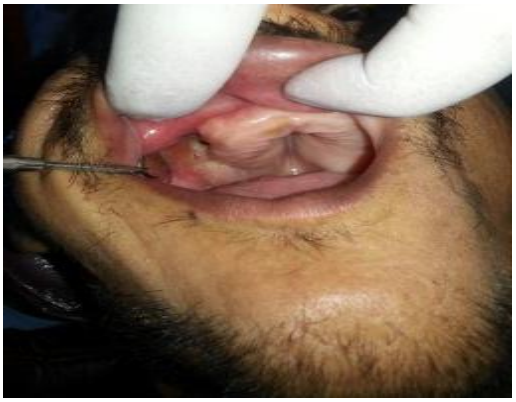

Figure 5: shows intraoral sinus at upper right molar area.

Figure 6: shows the female nephew with protrude maxilla and full dentition.

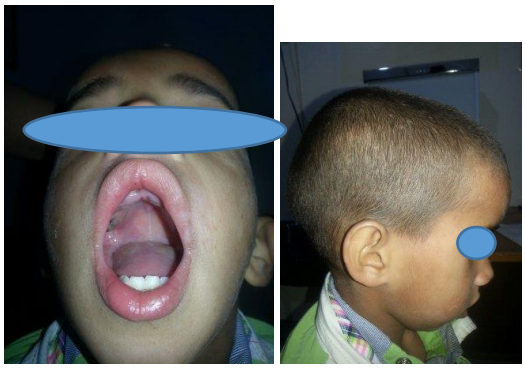

Figure 7: shows the patient's male nephew with maxillary decayed teeth and frontal bossing.

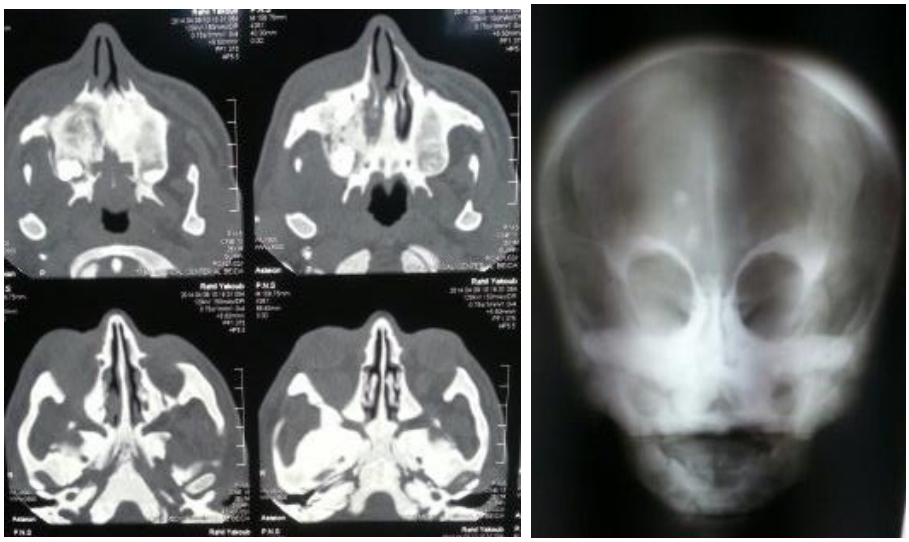

Figure 8: Coronal CT scan and PA skull views showed increased bone density especially at the skull base, zygoma, and maxilla with obliteration of paranasal sinues. On the right side of the maxillary bone, CT scan revealed bone irregularities that may indicate the bone seqestra.

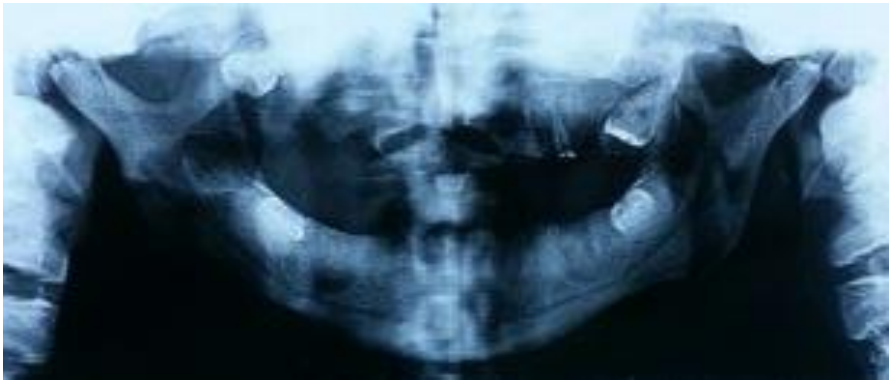

Figure 9: Orthopantomograph shows increased bone mass with obliterated nasal and paranasal cavities and also showed impacted wisdom teeth.

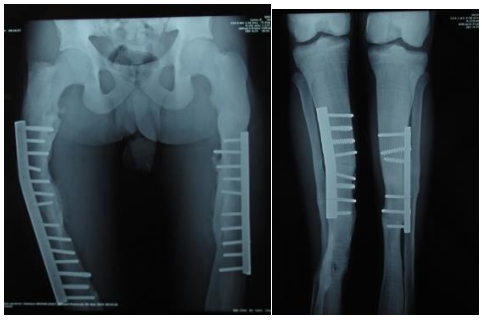

Figure 10: showed plated fracture of both femurs and tibias, with healed fracture at right tibia.

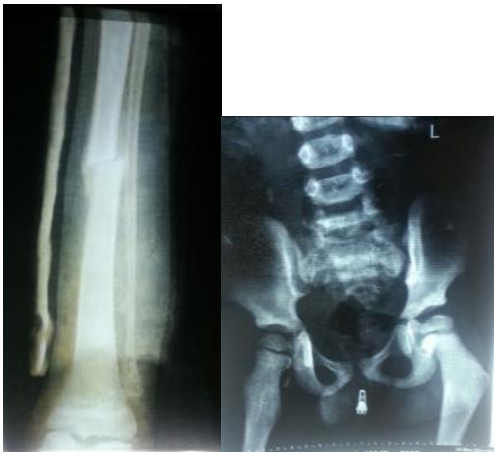

Figure 11: Casted fractured tibia and healed fractured femur of male nephew.

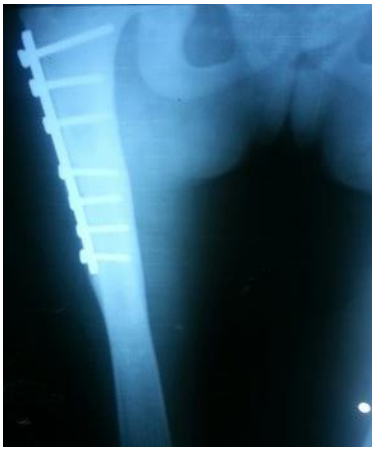

Figure 12: plated fractured femur of female nephew.

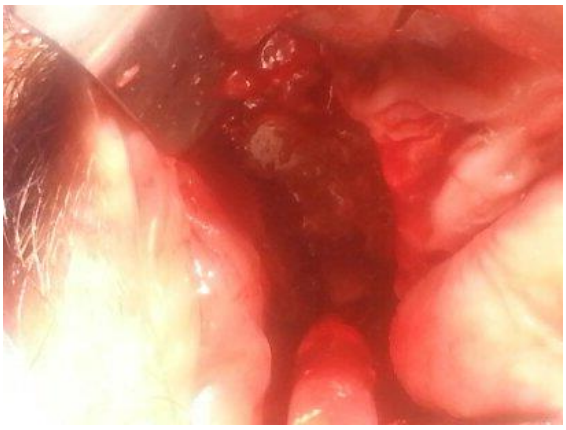

Figure 13: surgical site with dark bone without bleeding points