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Consanguinity Remains A Challenge: A Case Study And Algorithm On Malignant Osteopetrosis In A Paediatric Patient

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Abstract
Osteopetrosis is a class of rare hereditary skeletal illnesses characterised by a substantial rise in bone density brought by a decrease in normal osteoclast activity. A ten percentile of patients with osteopetrosis go on to develop osteomyelitis, which typically affects the mandible. Treatment of osteopetrosis stays complicated and often unsatisfactory. A 7-year-old male child reported with draining sinus wrt left mandibular arch. The child had associated cardinal general features of suspected osteopetrosis with suppurative osteomyelitis of mandible. This case report highlighted logarithm and unnoticed case of osteopetrosis born to consanguinous couple.

Keywords: Osteopetrosis, Marble bone disease, Albers-Schonberg disease, consanguineous marriage

Introduction
Osteopetrosis is a condition characterised by reduced osteoclast function. Heinrich Albers - Schonberg initially characterised it in 1904. Karshner coined the term in 1926 [1].

There are at least 9 kinds of Osteopetrosis, each with unique clinical and radiological characteristics [2]. Osteopetrosis was categorised by Schinz (1944) according to four genetic types:1. Simple-dominant: modest course with favourable prognosis,2. Simple-dominant with a malignant course that progresses,3. Simple-recessive-good prognosis and modest course,4. Simple-recessive-cancerous, with poor prognosis [3].
The categories of dominant-benign, dominant-malignant, recessive-benign, and recessive-malignant types were added to Schinz's classification by Hanhart [1948] [4].

The occurence of osteopetrosis is difficult to quantify. The annual birth ratio for autosomal dominant osteopetrosis and autosomal recessive osteopetrosis is 2,50,000: 20,000 [5].

Differential diagnosis-Malignancies (such lymphoma and osteoblastic carcinoma metastases), myelofibrosis, toxicity from bismuth, lead, and beryllium, and Paget's disease (sclerosing type) [6].

Treatment & prognosis - Management of infantile osteopetrosis is complicated since it remains undetected in most cases. If left untreated,leads to mortality within the first ten years of life [7].

This case report gives a detailed overview of a 7-year-old patient diagnosed with malignant infantile osteopetrosis with suppurative osteomyelitis of mandible born to consanguineous couple.

Case report:
A 7-year-old male patient with his parents reported to the Department of Pediatric and Preventive Dentistry. Their primary concern was swelling over left lower side of face with pus draining sinus which was soft in consistency with raised temperature in the last 4 months. **(Figure 1).**

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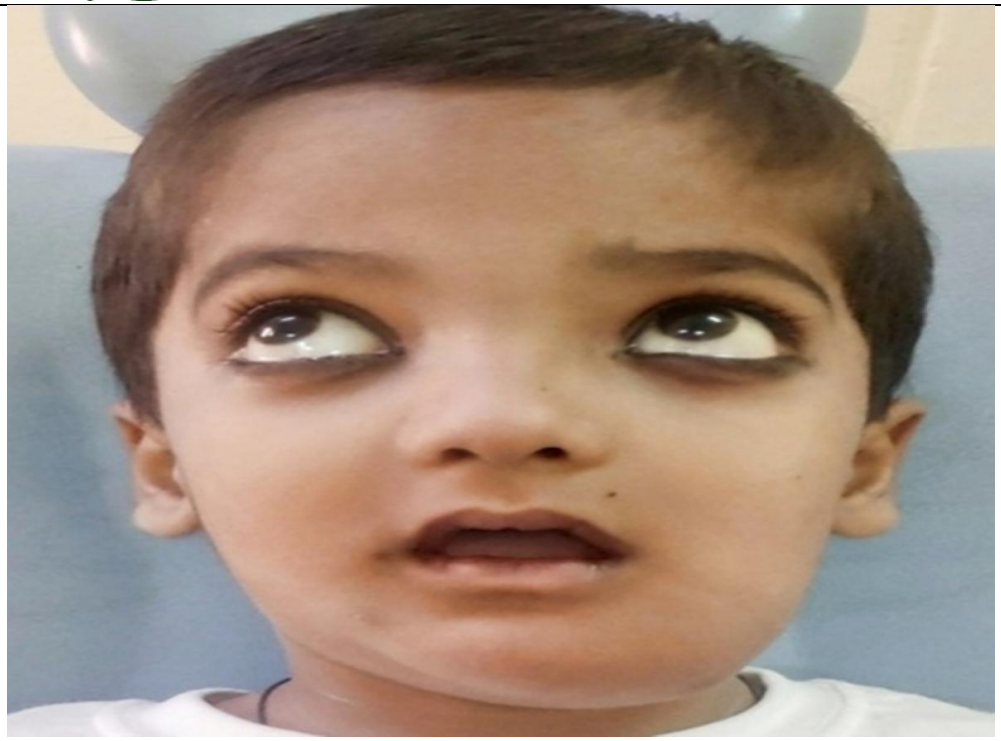
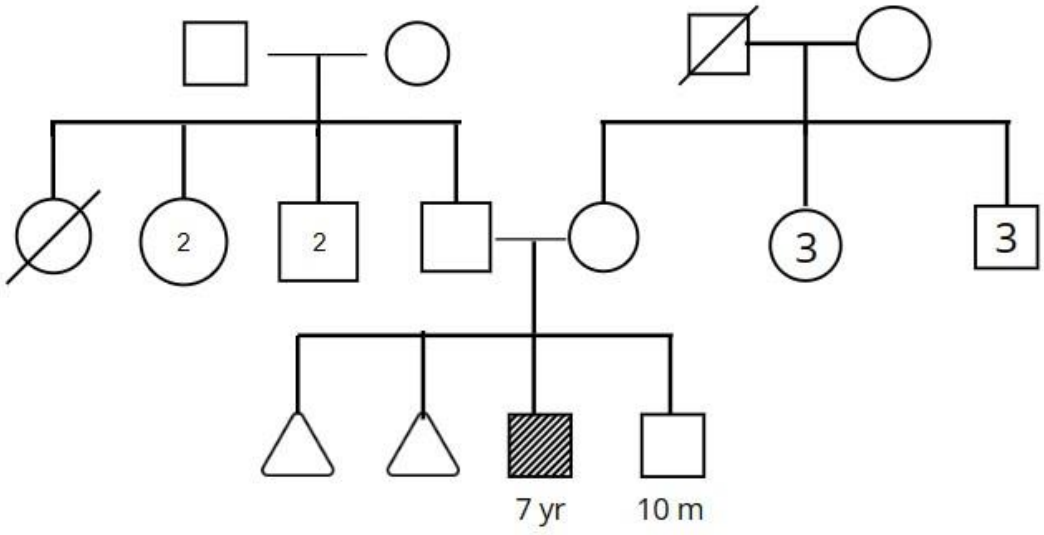


Figure 1: Osteopetrosis in 7-year-old child showing frontal bossing exophthalmus and hypertelorism

History of present illness- The parents reported that the swelling initially appeared as a small localized mass 2 months back in same region which progressively enlarged to the present size (5cm*5cm) associated with draining sinus.They also gave history of low grade fever since then.
The patient was well oriented, moderately built, behaved very well, respond to daily verbal communication. For daily activity patient was depended on this parent.

Medical History:

1. **Family History and pedigree:** Patient (III_1) born to a consanguineous marriage.
2.



Flowchart 1: Pedigree-Parents were first cousins (II_1:II_2).

The patient was the first child, and has a younger brother (III_2) who is 10 months old and in apparent good health.
2. Perinatal History: He was born through full-term lower segment cesarean section with a delayed cry.

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3. Postnatal history:

The patient had single seizure episode on the second day after delivery.

At six months of age, the patient's parents realised that his vision had reduced since he was not responding to any visual stimuli, such as smiling.

The patient was diagnosed with congenital optic atrophy at two years old. Simultaneously, a spontaneous fracture was observed in the right ulna's distal third shaft, accompanied by soft tissue edema.

He had a right femur shaft fracture when he was three years old. Concerns regarding potential systemic problems or underlying bone fragility were raised by these fractures.

Despite the patient having early-stage classical features of bone disease, the condition went undiagnosed and untreated.

General examination:

1.Head: Brachycephalic with frontal bossing

2.Vision: Signs of visual impairment, absence of pupillary response to light,bilateral exophthalmos and positive nystagmus.

3.Distended abdomen

4.Vital signs:Normal

5.Facial Asymmetry:Significant facial asymmetry due to swelling.

Intraoral examination: Maxillary and mandibular arch almost edentulous, Root stumps present irt 54,63,64, Decayed irt 85 and intraoral lesion present in respect to 73 regions. **(Figure 2A,2B)**.

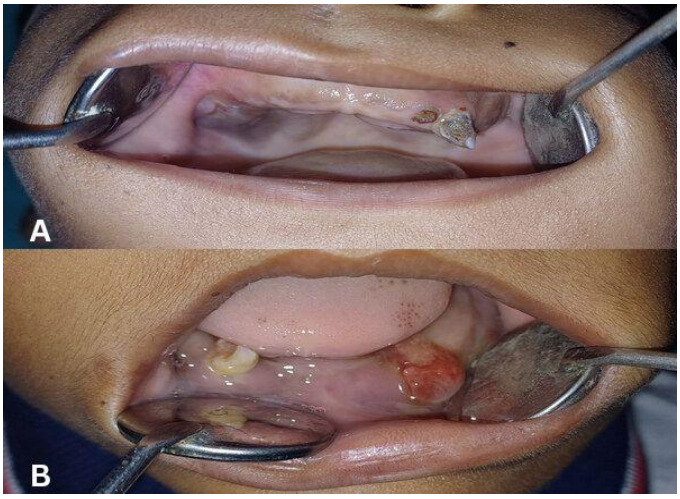

Figure 2: Intraoral examination A-Maxillary arch showing root stump irt 54,63,64 B-Mandibular arch showing sinus in left canine region

Patient referred to the Pediatric Department of Rohilkhand medical college and hospital, Bareilly for further radiological and laboratory investigations.

Diagnostic Investigations:

1.NCCT Face:

i. Generalised osteogenic lesion involving maxilla, bilateral maxilllary sinus, nasal cavity and mandible. Radiopaque patches of amorphous bone, with increased overall density of bone.

ii. Loss of cortical outline with asymmetric maxilla and mandible, expansion of buccal and palatal cortices

iii. Left side deviation of nasal septum

iv. Complete obliteration of maxillary sinus **(Figure 3)**.

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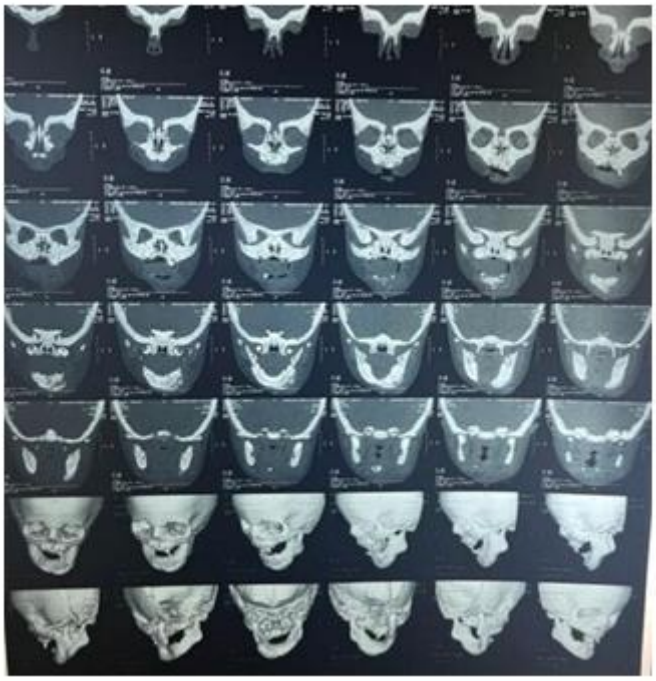

Figure 3: NCCT of face showing erosion of anterior cortex symphysis menti and body of mandible.

3. CECT Head-Dilated ventricles suggestive of non-obstructing hydrocephalus **(Figure 4).**

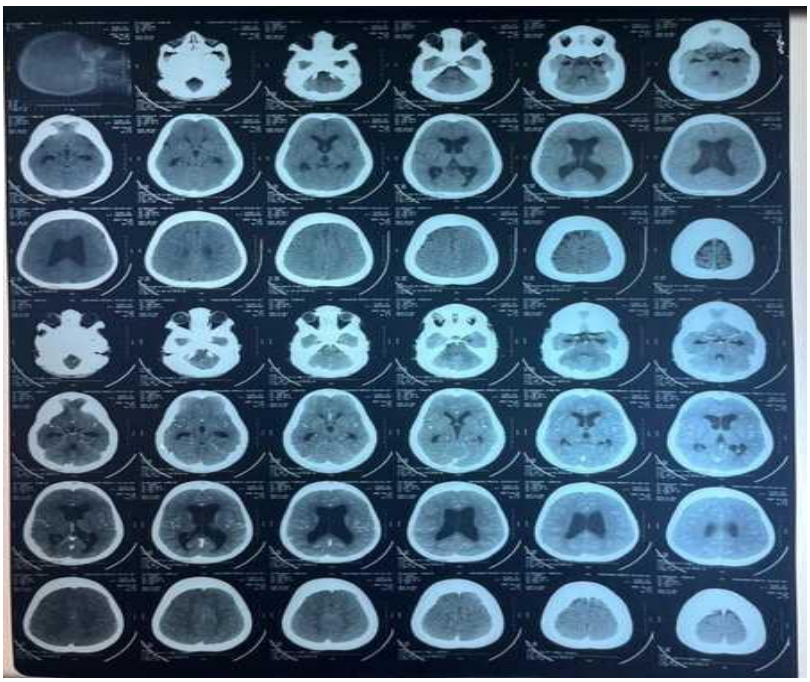

Figure 4: CECT showing dilated ventricles

3.Ultrasound Abdomen: Gross enlargement of spleen (approximately 16.5cm) suggestive of splenomegaly **(Figure 5)**.

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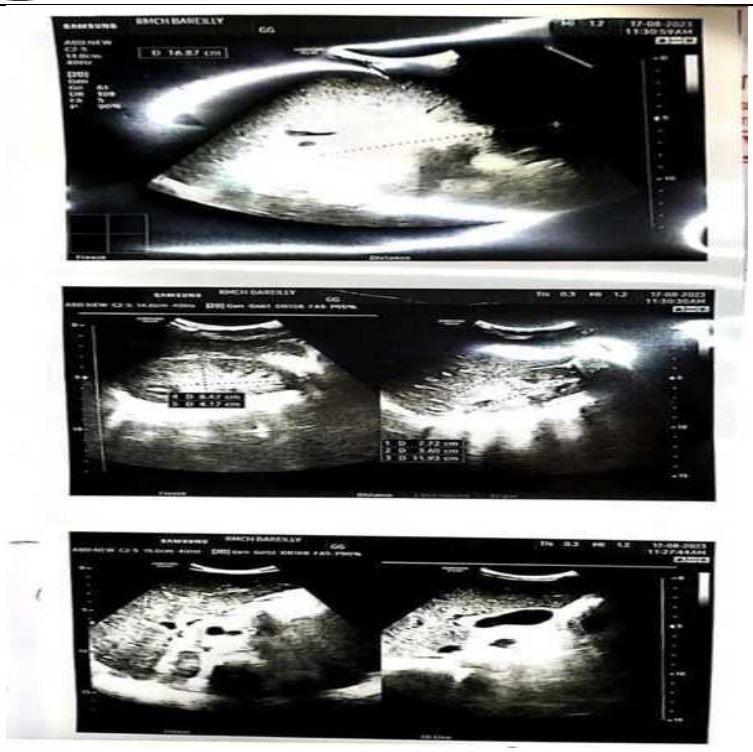

Figure 5: Ultrasound of abdomen shows gross enlargement of spleen

4.Orthopantamogram: Numerous impacted permanent teeth seen in both maxilla and mandibular arch **(Figure 6).**

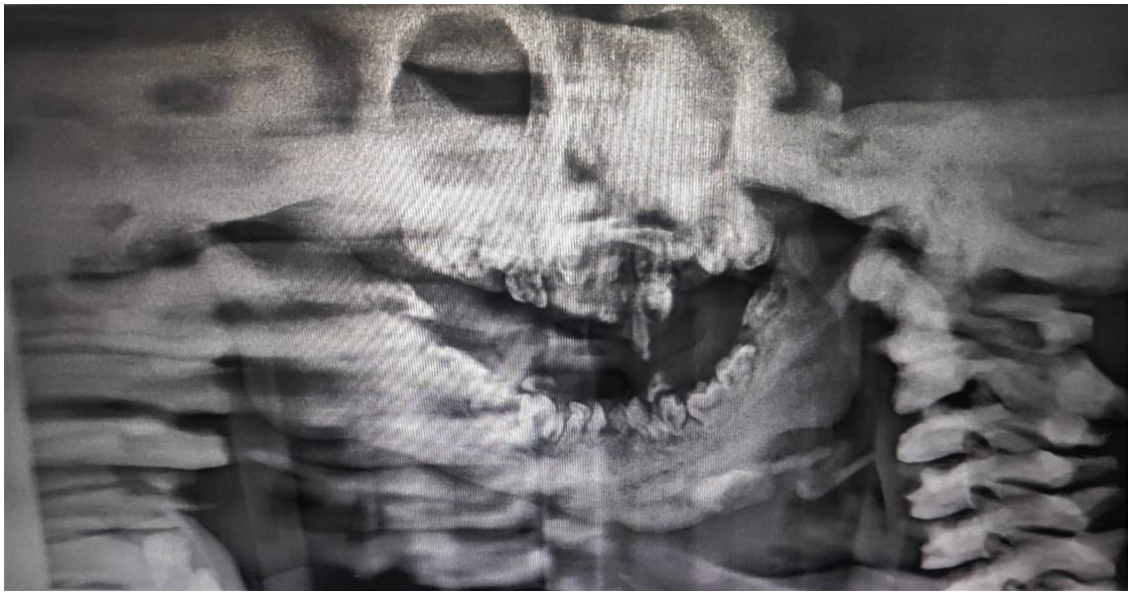

Figure 6: OPG shows numerous unerupted teeth in maxillary and mandibular arch

5. Skull X Ray PA view-Skull vault showed dense bone with narrowing of skull base and elongated head,thickening of cortical tables(**Figure 7).**

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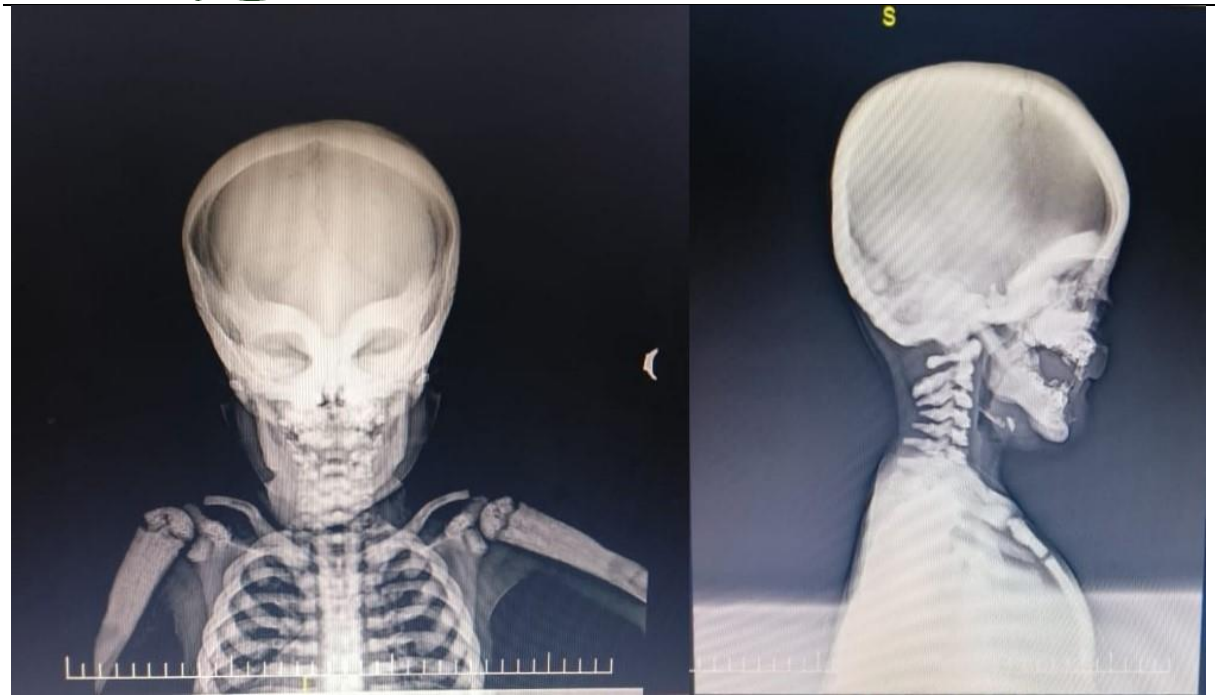

Figure 7: showing dense bone with narrowing of skull base and elongated head

6.Chest X Ray PA view: Thickening of costochondral junction, loss of bony corticomedullary differentiation, metaphyseal lucent bands **(Figure 8)**.

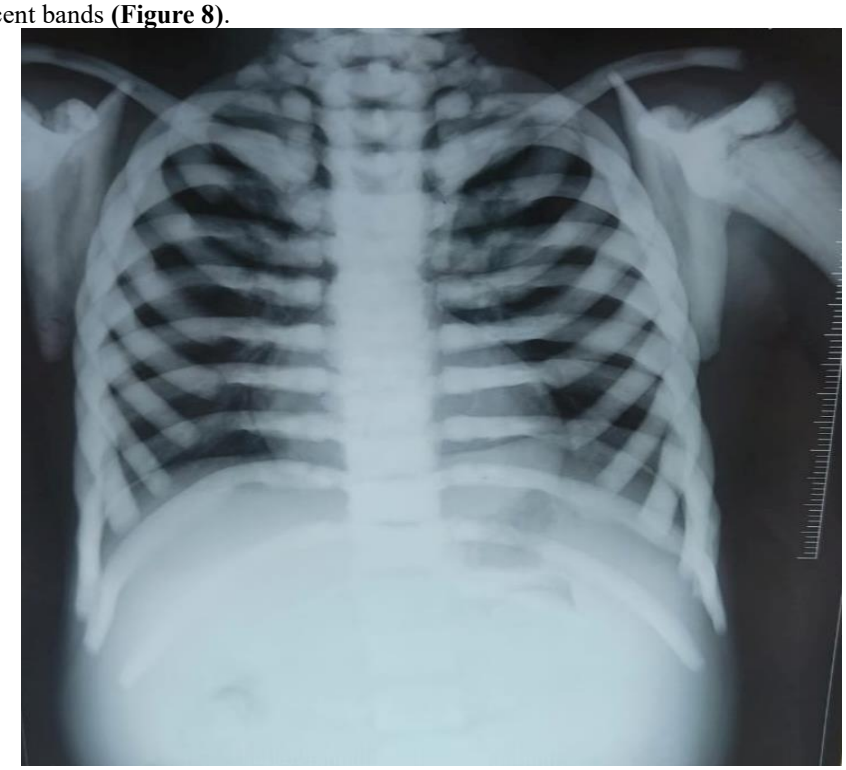

Figure 8:PA view of chest showing widened costochondral junction and enlargement of cardia

7. Hand wrist X Ray: Bilateral humerus showed a bone within bone appearance (**Figure 9).**

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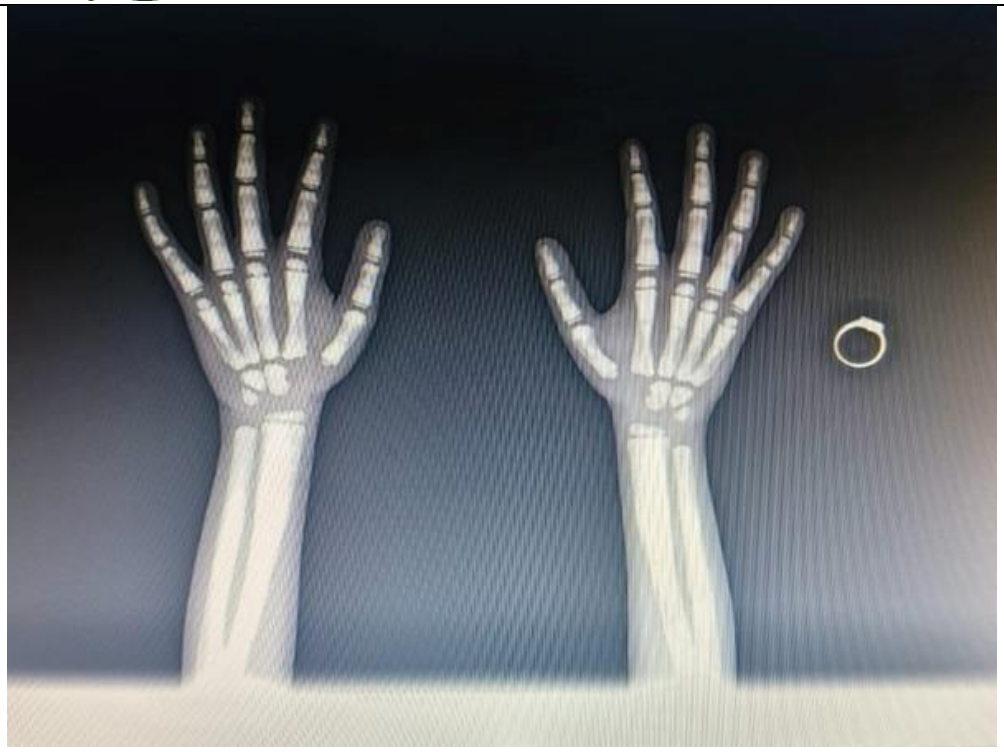

Figure 9: Hand X ray showing bone within bone appearance

8. Pelvic sacro X Ray: Pelvic lumbo sacral bone showed generalised increase in bone density **(Figure 10).**

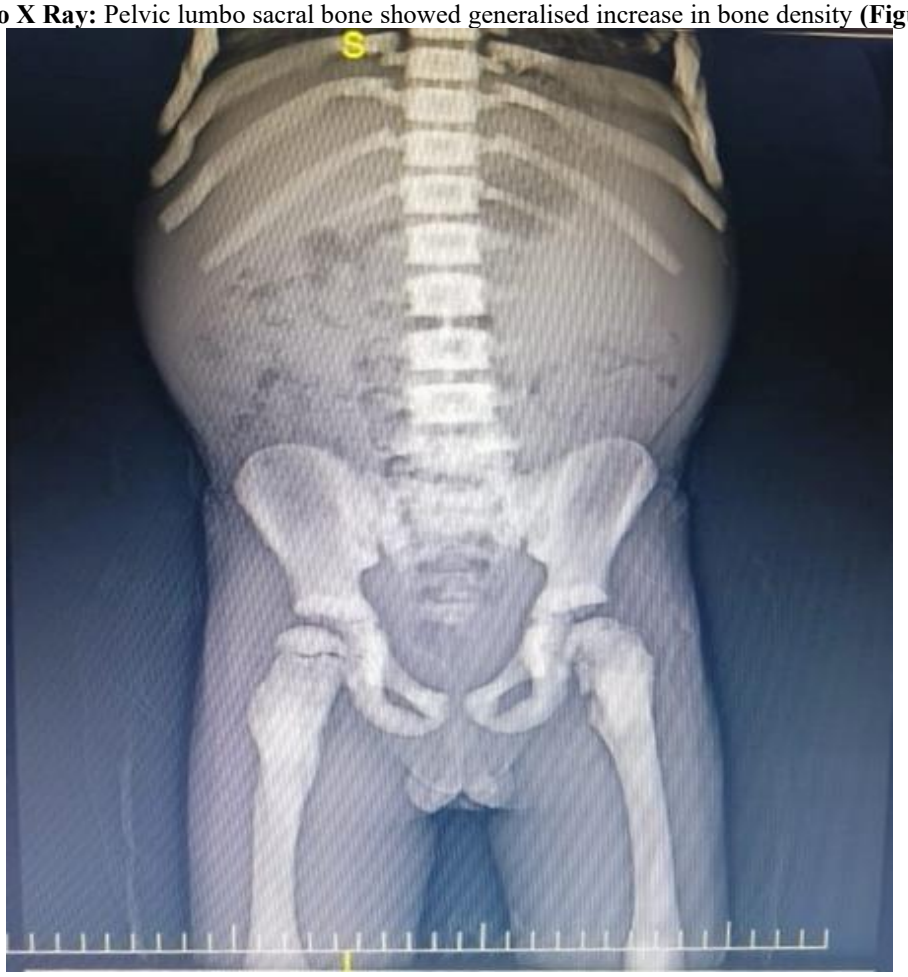

Figure 10: Pelvic lumbo sacral bone showing generalised increase in bone density

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(Table 1) Hematological Profile:

Test parameter	Normal Values	Observed Values
Haemoglobin	13-18g%	6.7g%
COAGULATION PROFILE- **Prothombin Time** **INR**	12.5-15.5 sec	15.7 sec 1.12
Total Red Blood Cell (RBC) Count	4.7-5.6 million/cu mm	2.7 million/cu mm
Total Leucocyte count (TLC)	4000-11000 per cu.mm	10,160 per cu.mm
Basophils	0-1%	0%
Polymorphs	40-75%	50%
Lymphocytes	20-45%	43%
Eosinophils	1-6%	2%
Monocytes	2-8%	5%
Mean Corpuscular Hemoglobin (MCH)	26-32pg	24.5 pg
Mean Corpuscular Hemoglobin concentration (MCHC)	30-35%	27.1%
Mean corpuscular volume (MCV)	80-100fl	90.5fl
Packed Cell Volume (PCV)	40-54%	24.7%
Platelet Count	1.5-4 lacs/cu.mm	0.80 lacs/cu.mm
RDW-CV	11-16%	23.1
RDW-SD	35-56fl	71.9fl
C-Reactive Protein (CRP)	6mg/dl	12mg/dL
Characteristics of red blood cells-Microcytic,hypochromic,polychromatophil,tear drop shaped red blood cells.		

(Table 2) Biochemical Examination:

Test parameter	Normal Values	Observed Values
Direct Serum Bilirubin	0.0-0.4gm/dl	0.63gm/dl
SGOT	10-40IU/L	52IU/L
Interpretation: Table 2 shows increased direct serum bilirubin and SGOT		

The radiological findings of head, face and body and laboratory finding (haematological and biochemical) suggest suspected osteopetrosis.

Since the patient was suffering from multiple complications and discuss the present condition with parents,we referred him to All India Institute of Dental Sciences, Delhi. (Supplementary file) Patient was undertaken on the emergency basis and abscess was drained out after 170ml packed RBC transfusion

Follow Up and outcome: When the patient was called after 15 days,but unfortunately parents reported that he succumbed to death.
The patient's parents gave their formal consent for photos and medical information to be used in publications.

Discussion:

A rare genetic bone condition called autosomal recessive osteopetrosis (ARO), its fundamental molecular basis is well understood. Lam CW et al advocated that mutated TCIRG1, CLCN7, or OSTM1 genes are responsible for ARO. The majority of ARO cases have been related to TCIRG1 gene mutations, with only a few instances attributable to CLCN7 gene mutations [8].

Consanguinity is a strongly ingrained societal pattern among one-fifth of the global populace, it varies from 14% to 16% in India [9,10]. In first degree related matings, the chance of birth abnormalities has increased to 5-8% from 2-3% in non-consanguineous marriages [11].

The death rate associated with untreated malignant infantile OP is over 75% by the age of 6 years, which is largely ascribed to bone marrow failure due to inadequate hematopoiesis [12]. Treatment is mostly supportive, focusing on interdisciplinary monitoring and symptomatic treatment of consequences.Different literature says Hematopoietic stem-cell transplantation (HSCT) and Interferon gamma 1b (IFN1b) can be tried in patients with osteopetrosis [6].

In this case, the kid was born from a consanguineous marriage and exhibited characteristic symptoms of osteopetrosis. To our knowledge, this case study is the first to present the osteopetrosis logarithm in connection to consanguinity (**Table 3) [8,13-18].**

Table 3: Logarithm of reported cases of osteopetrosis from consanguineous marriage (Search Engine-Pubmed, Mesh Term-Osteopetrosis, Consanguineous-marriage, Boolean enquiry-AND/OR.) Out of total n=77, (7 articles fulfilled the search criteria):

Sl No.	Author (year)	No of patients	Diagnosis	Outcome
1.	Ott CE et al (2013)[13]	2	Autosomal recessive osteopetrosis	Died
2.	Aker M et al (2012)[14]	4	Malignant osteopetrosis	1 died
3.	Stark Z et al (2012)[15]	1	Autosomal recessive osteopetrosis	Pregnancy terminated at 29 weeks
4.	Guerrini MM et al (2008)[16]	8	Autosomal recessive osteopetrosis	3-died 5-alive
5.	Souraty N et al (2007)[17]	6	Autosomal recessive osteopetrosis	4-died 1-alive 1-outcome not mentioned
6.	Lam CW et al (2006)[8]	1	Autosomal recessive osteopetrosis	Died at 9 months
7.	Borthwick K et al (2003)[18]	4	Autosomal recessive osteopetrosis	1-died 3-alive

Parents were unable to recollect any type type of medical or genetic disorder. To define this diagnosis, Karyotyping was also advised to the parents but due to the financial condition they could not afford it.

Conclusion:

Everything in life is impacted by the decisions we make and the beliefs we maintain. And we bear the ramifications of our decision in daily life. Consanguineous marriage is one example of a familial-social tie. Indians are more likely to get uncommon illnesses because of the custom of getting married within their own clan. The Union Ministry of Health and Family Welfare estimates that over eight crore Indians may be afflicted with uncommon diseases, which is a catch-all phrase for a range of more than 5000 illnesses, most of which have a hereditary basis. Thus, it is imperative to develop a multi-approach public health programme in a community with high levels of inbreeding.

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