Open Access Case Report

Repeated Failed Attempts of Bone Marrow Aspiration in an Infant

Nadeem Ikram[1]
Raana Zeeshan[2]
Wasia Salam[3]
Sundas Durrani[4]

[1-4]Department of Pathology Benazir Bhutto Hospital and Rawalpindi Medical University, Rawalpindi
.
Address for Correspondence
Dr. Nadeem Ikram
Department of Pathology Benazir Bhutto Hospital and Rawalpindi Medical University, Rawalpindi.
drnadeemikram@gmail.com

Abstract

Failed attempt of bone marrow aspiration can be anticipated in some cases. It can be resolved by bone marrow trephine biopsy. In an infant this occurrence of failed aspiration, even after repeated attempts can lend to a situation of not being able to make a diagnosis. In a child of less than one year age this situation can be ascribed to the site for trephine biopsy, not being mature at this age. Present case is a of similar nature where there were repeated failed attempts of marrow aspiration
Keywords: Bone Marrow Aspiration.

Case Report

A six months old male child presented with repeated chest infections, failure to thrive and progressive pallor with hepatosplenomegaly. He was febrile (102^{O} F). Respiratory rate was 65/min. Abdominal examination revealed hepatosplenomegaly. Respiratory examination revealed crepitations and ronchi. Investigations revealed leucoerythroblastic blood picture with haemoglobin with haemoglobin 7.2 g/dl,total leucocytes count 39400/mm^2 with differential count of neutrophils-30%, lymphocytes-44%,monocytes-02%, eosumphils -03%, promyelocytes-05%, myelocytes-08% and metamyelocytes-05%. Five nucleated red blood cells were seen against 100 white blood cells. Platelet's count was 50,000/mm^2. Peripheral blood smear revealed anisopoikilocytosis. Tear drop cells were seen. Reticulocytes count was 9.0%. Serum calcium level was 6.9 mg/dl. Haemoglobin electrophoresis revealed no haemoglobin disorder.

Bone marrow axamination was advised. Repeated (thrice) aspiration attempts from tibial tuberosity of both sides were failed. As per the age of child, we did not proceed for bone marrow trephine biopsy. As a result, bone marrow examination failed to give any diagnosis. In the meantime, his X-ray chest was performed due to repeated chest infections. Incidentally X-ray revealed increased bone density in ribs. Subsequently skeletal survey revealed increased bone density in different bones of body (Figures 1-4). He was diagnosed as a case of osteopetrosis (Malignant Infantile Osteopetrosis; M.I.O.P)

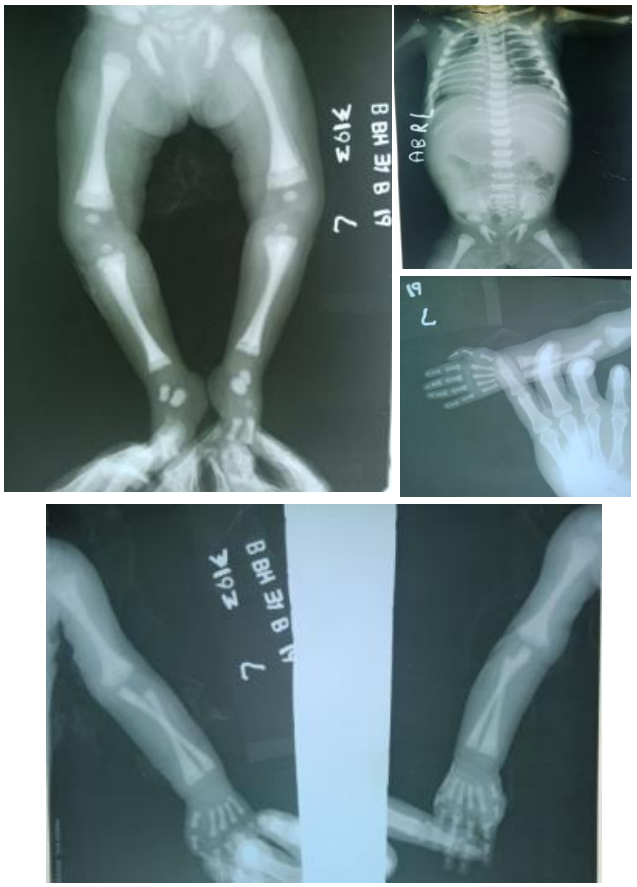

Figure 1-4. Skeletal survey report: There is an increase bone density of both humerus, radius, ulna, femur, tibia, fibula, spines and ribs. There is expansion of the visualized both femur, tibia and ribs. There is hepatosplenomegaly, which needs ultrasonographic correlation

Discussion

Osteopetrosis (O. P), also labeled as Marble Bone Disease, is a rare genetic disorder characterized by functional defect of osteoclasts resulting in failure of bone resorption, increased bone sclerosis and bone marrow failure.[1-3] The name of the disease derived from "Osteo" means bone and "petro" means stone.It may be inherited as autosomal dominant, autosomal recessive or intermediate inheritance pattern. Autosomal recessive O.P, also known as Malignant Infanatile Ostepetrosis (M.I.O.P), is the most severe form and manifests in first few months of life (Table I).[4] M.I.O.P generally starts in intrauterine life and manifests at birth or early infancy. [5] Autosomal dominant form is usually asymptomatic. It is diagnosed incidentally or may exhibit mild symptoms in late childhood or adult life, but is compatible with long term survival. [6]

Clinical presentation varies widely, based on the type of osteopetrosis and ranges in severity from asymptomatic to a fatal course. [4] Autosomal recessive MIOP is uncommon. Classic autosomal recessive MIOP is characterized by repeated infections, fractures, stunted growth, compressive neuropathies, hypocalcemia with attendant tetanic seizures, and life threatening cytopenias and characteristic radiological findings.[7] It is a severe fatal disorder. Cranial nerve entrapment neuropathies occur due to failure of the foramina in skulls to widen completely. Manifestations include deafness, visual impairment, proptosis and hydrocephalus. [8] There is gradual obliteration of marrow cavity by both bony encroachment and associated fibrosis. Although bone density is increased, the bone is more fragile than normal. [9]

Risk of developing haematological impairment in the first year of life is about 75% and its onset within three months of life is indicative of poor outcome.[2,10] Failure to thrive and increased infections because of an unexplained defect in neutrophils superoxide function are also characteristic. [11]

The abnormal expansion of bone osteoid in autosomal recessive O.P interferes with medullary haematopoiesis, resulting in life threatening pancytopenia with secondary expansion of extramedullary haematopoiesis at sites such as liver and spleen, thereby leading to hepatosplenomegaly. [7] The expanding bone can narrow nerve fragments resulting in signs of nerve compression, such as blindness, deafness, facial palsy.[4] The increase in bone density paradoxically weaken the bone, resulting in a predisposition to fractures and osteomyelitis. The longitudinal growth of bones is impaired, resulting in short stature. [7]

In present case hypocalcaemia is documented. Disturbances in calcium metabolism are well documented in O.P. In the neonatal period, children are relatively hypothyroid. In this setting normal osteoblasts function, unchecked by compensatory osteoclasts, is likely to push osteopetrotic children into hypocalcemia.[12]Hypocalcemia, hypophosphatemia and secondary hyperparathyroidism are noted in the absence of hypovitaminosis –D.[4,12,13,14]

Mutations in at least 10 genes have been

Table I: Types of Osteopetrosis

Characteristics	Infantile	Intermediate	Adult
Inheritance	Autosomal Recessive	Autosomal Recessive	Autoso-mal dominant
Genetic Basis	TCIRG, CLCN7 mutations	CLCN7, PLEKHM1 mutations	CLCN7 mutations
Diagnosis	Before age of one year	Incidentally	Incident-ally
Skeletal manifestations	Increased bone density; diffuse and focal sclerosis of varying severity;modelling defects at metaphyses; pathological fractures;osteomyelitis; dental abnormalities; tooth eruption defects; dental caries		
Haematological Manifestations	Pancytop-enia;Extramedullary haematop-oiesis; hepatospl-enomegaly	Anaemia & extramedullary haemtopoiesis	Mode-rate haema-tological failure
Neurological problems	Cranial nerves compre-ssion (II;VII; VIII)	Occasional optic nerve compression	Occasional optic nerve comp-ession
Other findings	Hydrocephalus; stunted growth; hypocal-caemia		
Onset	Perinatal	Childhood	Late child-hood or adolescence
Severity	Severe	Mild to moderate	Mild to moder-ate
Treatment	Supportive;HSCT*	Supportive	Suppo-rtive
Prognosis	Poor;fatal in infancy	Variable	Normal life expect-ancy
Recurrence risk	Parents of probond: 25% risk of recurrence in future pregnancies	Parents of probond: 25% risk of recurrence in future pregnancies	50% in future pregnancies if one parent is affected

*HSCT=Haemopoietic Stem Cell Transplantation

identified.[15] M.I.O.P involves mutation in TCRIG1 (ATPG1) encoding the a3 subunit of the vacuolar proton pump.[16,17] The primary underlying defect in all types of osteopetrosis is failure of osteoclasts to resorb bone resulting in thickened sclerotic bones, which have poor mechanical properties. It affects all bones in human body.[18] Increased bone fragility results from a failure of the collagen fibers to convert ostean properly and from defective remodeling of weven bone to compact bone.[7,2] Paradoxically increase in bone density weakens the bone, resulting in a predisposition to fractures and osteomyelitis. The longitudinal growth of bones is impaired, resulting in short stature.[7]

Defective genes in O.P are involved in the acidification machinery. Acid secretion is dependent on two key molecules, which facilitate proton transport: the proton pump vacuolar ATPas) V-ATPase) and chloride specific ion channel, chloride channel 7 (CLCN -7). Homozygous mutations in the gene encoding the a3 subunit of V-ATPase (TCIRG1) and CLCN-7 produce severe malignant O.P phenotype.[7]

Increased bone fragility results from a failure of collagen fibers to connect osteon properly and from defective remodeling of woven bone to compact bone, This leads to generalized sclerosis of bone with an increased skeletal mass. [8] Repeated infections in M.I.O.P are attributed to suppression of normal marrow haemopoiesis and unexplained defects in neutrophil superoxide function.[11]

Generalized osteopetrosis is apparent radiologically with increased bone density, often with a " bone within bone" appearance or a club like appearance. Increased bone density, diffuse and focal sclerosis of varying severity, modelling defects at metaphyses can be identified in almost all bones of the body. Pathological fractures, osteomyelitis, dental abnormalities, tooth eruption defects and dental caries are also frequent Radiographs of femur can show Erlenmeyer flask deformity. Just after birth infant may show lucent bands in distal ulna and radius Spine radiographs show sclerosis of vertebral endplates, resulting in 'sandwich vertebrae' appearance.[7].X-ray chest, in addition to bone density, may show widening at the costochondral junction.[5,15,18]

In severely affected patients the medullary cavity is filled with endochondral new bone with little remaining for haematopoietic cells.[14,19] The expanding bony trabaculae obliterate marrow, leading to bone marrow failure and a failed attempt of marrow aspiration. In an infant it can lead to a problem where it is difficult to get bone marrow trephine biopsy. On bone marrow trephine biopsy,the bony trabaculae appear thickened due to increased amount of mature lamellar bone with osteoclasts being prominent in some cases. The marrow intertrabacular spaces are occupied by connective tissue. There is loss of distinction between cortex and trabaculae. [9]

Regular ophthalmic surveillance including visual evoked potential (VEPs) is important in detecting optic nerve atrophy. Surgical decompression of the optic nerve can be employed to prevent visual loss. [20]

Pre-implantation and prenatal diagnosis is theoretically possible in families in whom the genetic mutations has been identified, thus allowing for reproductive decisions to be made. In families with severe severe autosomal recessive O.P and unknown mutations, pre-natal diagnosis may be possible using radiographs.[21] If a family decides to continue with an affected child, haematopoeitic stem cell transplantation (HSCT) before the age of three months can be planned with the aim of improving neurological outcomes. Once neurological complications emerge they cannot be reversed even after HSCT. [7]

At present, other than HSCT, at large treatment is supportive. Fractures and arthritis are common and require meticulous treatment due to brittleness of the bone and relatively frequent occurrence of secondary complications such as delayed union or non-union of fractures and osteomyelitis.[22]

Bone marrow transplantation (BMT) or Hemopoietic stem cell transplantation (HSCT) is the only curative option. It is better to contemplate HSCT before the emergence of complications, as it cannot reverse neurological complications. The best time is within one year of birth, more preferably within first few months of life. Recipients of HLA identical BMT or HSCT have been reported to have five years survival of 73 to 79%.[12,23-25]

Interferon gamma (IFN γ Ib) treatment has been reported to result in improvement in immune function, increased in bone resorption and increased in bone

marrow space.[26,27] Inteferon gamma therapy has been found to decrease the rate of infections and transfusion requirements after 24 months of therapy.[24]

Ongoing research into osteoclast physiology is likely to result in novel therapeutic targets. For example, low levels of bone resorption are observed in even severely affected patients, pointing to the presence of multiple acidification mechanisms. The activation of alternate acidification including he Na+/H+ antiporters have been proposed as therapeutic targets.[28]

Bubshalt DK et al reported a case of M.I.O.P who presented at the age of two months with a history of recurrent fever, recurrent pneumonia, developmental delay and infantile spasms . Upon exmiantion found to have hepatosplenomegaly, axial hypotonia, limb spasticity and visual impariement.[5] Local data search revealed pool apart spectrum of O.P, justifying inheritance pattern. Asif N et al (2012) documented an infant of M.I.O.P with widespread skeletal changes, hepatosplenomegaly and marrow failure. [2] Ahmed S (2008) reported an adult soldier whose X-rays incidentally revealed end plate sclerosis of thoracic vertebral bodies (Rugger-Jersey- Spine). He did not show any skeletal, haematological and neurological findings which can be ascribed to sclerosis. [8] In MIOP prompt diagnosis and earliest bone marrow or HSCT (transplant within six months of age) ensures cure and circumvents visual, auditory and other defects which are not likely to be recovered if transplant is delayed. Prenatal molecular and/or radiological screening needs exploration.[12,25,29] Repeated bone marrow aspiration failure in an infant called for to rule out a rare occurrence of osteopetrosis, as is evident from this case report.

References

1. Mazzolari E, Forivo C, Razza A, Porta F, Villa A. A single center experience in 20 patients with infantile malignant ossteopetrosis.Am J Hematol, 2009;84: 473-79
2. Asif N, Hassan K, Akram U, Farooq MA. Osteopetrosis –a rare cause for bone marrow failure. Journal of Islamabad Medical and Dental College,2012;2:99-101
3. Superti-Furga A. US and the Nosology Group of the International Skeletal Dysplasia Society: Nosology and Classification of Genetic Skeletal Disorders .American Journal of Medical Genetics, 2007;143(A):1-18
4. Wilson CJ, Vellodi A. Autosomal osteopetrosis; diagnosis, management and outcome .Arch Dis Child, 2000;83:449-52
5. Bubshait DK, Himdy ZE, Fadaq O, Alshmas HI. Malignant infantile osteopetrosis : A case report. Cureus ,2020; 12(1): e6725-e31
6. Phadke SR, Fischer B, Gupta N, ranganath P. Novel mutations in Indian patients with autosomal recessive infantile malignant osteopetrosis. Indian J Med Res, 2010; 131: 508-14
7. Stark Z and Savarirayan R. Osteopetrosis . Orphant Journal of Rare Diseases, 2009;4(5):1750-612
8. Ahmed S, Uttra K, Adult osteopetrosis. Pak Armed Forces Med J, 2002; 58(4): 467-69
9. Bain BJ, Clark DM, Wilkin BS. Diseases of bones. In Bone marrow pathology,2012; 4th ed; 595-96
10. Komar Jk, Bandarn K, Prashanth SN, Mamatha S.Malignant infantile osteopetrosis . Indian J Hum Gen, 2013;19(1): 90-92
11. Key LLJ, Ries L, Rodriguiz RM, Hatcher HC. Recombinant human interferon gamma therapy for osteopetrosis. J Pediatr, 1992; 121: 119-24
12. Srinvasan M, Abinun M, Cant AJ, Tan K. Malignant infantile osetopetrosis presenting with neonatal hypocalcemia . Arch Dis Child Fetal Neonatal,2000; 83: F-21-F23
13. Nour M. Infantile malignant osteopetrosis . J Pediatr , 2013; 163: 1230-31
14. Dozier TS, Duncan IM, Klein AJ, Lambert PR. Otologic manifestations of malignant osteopetrosis . Otol Neurotol , 2005; 26: 762-66
15. Shapiro F. Osteopetrosis :current clinical consideration . Clin Orthop , 1993; 34-44
16. Gosawami R, Primer on the metabolic bone disease and disorders of mineral metabolism. Indian J Med Res, 2016; 144: 489-91
17. Kalekan T, Sehranat V. Autosomal recessive infantile osteopetrosis :case report with radiological review. Int J Res Med Sci, 2017;5(10): 18203/06
18. Rose Mery S, Pharm D, Winfred C, Jerome W. Malignant infantile osteopetrosis . Otolaryngical complications and management . Arch Otolaryngeal Head Neck Surg, 1998; 124(6):589-94
19. Jakub T, Steven L, Teitelbanm. Osteopetrosis . N Eng J Med, 2004; 351:2839-49
20. Hwang JM, Kim IO, Wang KC. Complete visual recovery in osteopetrosis by early optic nerve decompression . Pediatr Neurosutg, 2000; 33: 328- 32
21. Ogur G, Ogur E, Celasun B, Baser I. Prenatal diagnosis of autosomal recessive osteopetrosis , infantile type by X-ray evaluation . J Am Acad orthop Surg, 2007; 15: 654-62
22. Landa J, margolus N, Di Cesare P. Orthopaedic management of the patients with osteopetrosis . J Am Acad Orthop Surg, 2007; 15: 654-62
23. Driessen GJ, Gerritsen EJ, Fischer A, Fasth A. Long term outcome of haemopoietic stem cell transplantation in autosomal recessive osteopetrosis ;an EBMT report .Bone Marrow Trasnplant, 2003; 32: 657- 63
24. Gerritsen EJA,Vossen JM, Fasth A, Friedrich W. Bone marrow transplantation for autosomal recessive osteopetrosis ;A report from the working party on inborn errors of the European Bone Marrow Transplantation Group. J Pediatr,1994; 125:896-900

25. Solh H, Da CA, Giri N. Bone marrow transplantation for infantile malignant osteopetrosis . j Pediatr Hematol Oncol, 1995; 17:350- 55

26. Lyseng – Williamson KA. Interferon gamma- Ib in chronic granulomatous disease and severe malignant osteopetrosis . Drug Ther Perspect, 2015; 31: 213-20

27. Kelly LL, Rodriguiz RM, Willi SM, Wright NM. Long term treatment of osteopetrosis with recombinant human interferon gamma. N Eng J Med , 1995; 332; 1594-99

28. Villa A, Guerrini MM, Cassani B, Pangrazio A. Infantile malignant , autosomal recessive osteopetrosis: the rich and the poor. Calaf Tisu Int ,2008

29. Driessen GJ, Gerritsen EJ, Fischer A, Fasth A. Long term outcome of haemopoietic stem cell transplantation in autosomal recessive osteopetrosis ;an EBMT report .Bone Marrow Transplant, 2003; 32: 657- 63