CASE REPORT

Association of possible osteopetrosis with acute myeloid leukaemia in a child

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SUMMARY

Osteopetrosis is a rare disease characterised by an increase in bone mass, skeletal malformations and bone marrow failure due to defective bone resorption. We report a 3-month-old male child presented with chest infections, failure to thrive and hepatosplenomegaly and diagnosed with osteopetrosis associated with acute myeloid leukaemia M₃ type (AML-M₃). The patient died on day 7 of admission due to respiratory failure. To our knowledge, this is the first case where both osteopetrosis and AML is diagnosed in a patient.

BACKGROUND

Osteopetrosis is a rare autosomal recessive disorder affecting jaw bones and teeth due to defects in osteoclast's resorption. The defect in resorption of osteoclasts could arise either from failure in differentiation or inability to perform resorption by mature, multinucleated but non-functional cells.¹ The differentiation defects have been linked to mutations in *RANKL* as well as *RANK* gene. In humans, defects also involve mutations in genes expressing proteins involved in the acidification of osteoclast subcellular compartment, a process necessary for proper bone resorption.^{1 2} In this case, we report a 3-month-old male child, who presented to us with failure to thrive, anaemia and hepatosplenomegaly and was later diagnosed with osteopetrosis with acute myeloid leukaemia (AML-M₃). Though blasts may be found in the peripheral blood smear of these patients, its association with AML is unreported.

CASE PRESENTATION

A 3-month-old male child, delivered preterm at 34 weeks, presented to us with failure to gain weight since birth, abdominal distension and recurrent episodes of fever, cough and breathlessness for 1 month. He was treated for bronchopneumonia in a private hospital and discharged after partial improvement 1.5 months previously. There was no history of consanguinity in family. Parents and another 12-year-old sibling were normal.

On examination, he had severe pallor at admission. His weight was 52% of expected and crown-wheel length and head circumference were 90% of expected. Weight for height was 80% and mid-arm circumference was 8.4 cm. Social smiles and neck holding were absent. There was bilateral axillary and inguinal lymphadenopathy. He was febrile (39°C) with respiratory rate of 70/min and had severe retractions of the chest wall. Auscultation of the chest revealed bilateral fine crackles. The liver

was enlarged 4 cm below the costal margin in the mid-clavicular line (liver span: 9.6 cm) and the spleen; 4 cm below costal margin and firm. The right-sided hydrocele was also present. Other systemic examinations were unremarkable.

INVESTIGATIONS

Investigations showed haemoglobin 6.5 g/dL; total lymphocyte count 86 700/mm³; differential leucocyte count: neutrophil 8%; blasts 88%; myelocytes 4%; and the platelet count 33 000/mm³. The peripheral smear of blood showed leucocytosis with a majority of cells as blast cells (figure 1). Blasts were myeloperoxidase positive but Sudan black negative. Red blood cells (RBC) showed macrocytosis with fair number of nucleated RBC. Platelets were also markedly reduced.

Bone marrow biopsy showed majority of cells as myeloblasts; suggestive of AML-M₃ type (figure 2). His reticulocyte count was 2% and coomb's test was negative. His prothrombin time and activated partial thromboplastin time were 18 and 62 s, respectively. His arterial blood gases (pH 7.41, bicarbonate 21.4 mEq/L, PaO₂ 62 mm Hg, PaCO₂ 28 mm Hg and base excess 4) blood urea (14 mg/dL), creatine (0.46 mg/dL), calcium (2.26 mmol/L), magnesium (0.62 mmol/L) and electrolytes (sodium 137.2 mmol/L, Potassium 3.82 mmol/L) were normal. TORCH screening and ELISA for HIV screening was negative. His acid phosphatase level was within normal range. Routine examination of the urine including pH, thyroid function test and tandem mass screening for metabolic diseases were normal.

Chest radiograph showed patchy opacities in all lung fields with generalised increase in bone density. A babygram of the child was performed that showed a generalised increase in the density of bones (figure 3).

Immunophenotyping from blood revealed that blasts were hypergranular with high-side scatter properties and positive for heterogeneous CD13 and bright CD33 pattern 1 with lack of CD 34, features consistent with diagnosis of acute promyelocytic leukaemia. Mutational analysis could not be conducted. A diagnosis of osteopetrosis with AML-M₃ type and bronchopneumonia was made. Karyotyping of the patient was not performed.

DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis includes carbonic anhydrase II (CA II) deficiency syndrome, which is an autosomal recessive disorder that produces osteopetrosis, renal tubular acidosis and

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Figure 1 Peripheral smear of blood showing myeloblasts.

cerebral calcification.³ Other features include developmental delay, short stature, cognitive defects and a history of multiple fractures by adolescence. The absence of seizure, normal arterial blood gases and urinary pH abnormal peripheral blood smear findings and suggestive bone marrow biopsy in our patient excludes CA II deficiency syndrome. Other differential diagnosis of increased bone density includes renal osteodystrophy, pyknodysostosis, Caffey's disease, fluorosis and hypervitaminosis A and D.

TREATMENT

The patient was treated with cefotaxime and amikacin since time of admission, packed red cells transfusion and platelet transfusion on day 2 and chemotherapy was planned to start on day 7 after getting report of bone marrow biopsy and immunophenotyping.

OUTCOME AND FOLLOW-UP

The patient suddenly deteriorated on day 6 of admission and developed respiratory failure as evidenced by arterial blood gas report: PaO₂ 32 mm Hg; PaCO₂ 86 mm Hg and HCO₃⁻; 9 mEq/L. He was put on mechanical ventilation but died on day 7. We could not do autopsy as the parents did not give consent for the same.

DISCUSSION

The incidence of osteopetrosis is 1/300 000 live-births. But it may be autosomal dominant which is the mildest form.^{4 5} The differentiation defects have been linked to mutations in *RANKL* as well as *RANK* gene; other than five previously reported gene

Figure 2 Bone marrow biopsy showing clumps of myeloblasts.

Figure 3 Babygram showing generalised increase in bone density.

in humans, that is, *CA-II*, *TCIRG1*, *C1CN7*, *OSTM1* and *PLEKHM1* are responsible for effector's function osteoclasts.¹ In our patient, parents and sibling are normal and there is no family history, the possibility of autosomal recessive malignant infantile osteopetrosis is the most likely possibility.

Affected children usually present in the first 3 months of life with failure to thrive and recurrent infections as in our patient. Children usually have severe pallor and bleeding tendencies due to low platelets. Fractures, nasal congestion and abnormal facies are common due to bony abnormalities. Features of cranial nerve dysfunction due to nerve entrapment may be present.⁶ Hepatosplenomegaly is invariably present because of the persistence of extramedullary hemopoiesis. Our patient has severe anaemia, hepatosplenomegaly and failure to thrive.

Marrow failure is common in osteopetrosis due to lack of normal medullary cavity in bone. A few blasts may be found in the periphery as these are thrown in peripheral blood from sites of extramedullary haemopoiesis but AML has not been reported in literature. AML in our patient may due to spontaneous mutation in the genes. As mutational analysis had not been conducted in this patient, we are not able to exactly pinpoint the reason of occurrence of acute myeloid in this patient.

A radiograph of the child is usually diagnostic and shows a symmetric increase in the bone mass with thickening of cortical as well as trabecular bone. This gives the solid appearance of the bone, that is, 'marble bone disease'. Hypocalcaemia may be found and tartarate resistant acid phosphatase levels in the blood are elevated.⁷

Treatment options include stem cell transplantation and γ -interferons but the prognosis of the infantile variety of the

disease is very poor as in our patient.⁸ Osteopetrosis is a very uncommon disease and its association with AML has not been reported so far.

Learning points

- Osteopetrosis is rare autosomal recessive disorder.
- Failure to thrive, recurrent chest infections and hepatosplenomegaly are common presentations.
- Acute myeloid leukaemia with osteopetrosis is unreported.

Contributors UKS and RP had drafted the manuscript. OPM and BPJ had conducted the literature review and provided intellectual input in writing the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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