## CLINICAL QUIZ (p292) ANSWER

In the patient's chest radiograph and subsequently his skeletal survey (Figure in the Question and Figures B, C, D), there was generalised increase in bone density with bone expansion and obliteration of marrow space. The classical "bone-in-bone" appearance and "sandwich vertebrae" were most apparent in the metacarpal bones and the lateral spine X-ray respectively.

The peripheral blood smear (Figure A) showed presence of nucleated red cells and immature white cells, which constituted a leucoerythroblastic blood picture. In addition, polychromasia and teardrop poikilocytes were found. There were no other abnormal cells in circulation to suggest a malignant disease.

Trephine biopsy (Figure E) showed marked increase in bone volume with thickened bone trabeculae and lack of normal laminated appearance; osteoblasts and osteoclasts were scarce and Howship lacunae were not seen. The narrowed marrow spaces were occupied by unmineralised osteoid.

The overall clinical picture was compatible with the diagnosis of osteopetrosis, of intermediate severity, and osteoclast-poor subtype. Subsequent to the diagnosis, the patient was dependent on 3-weekly transfusion. Magnetic resonance imaging of the cranium was significant for mild narrowing of superior orbital fissure, with crowding of optic nerves and extra-ocular muscles at apices as well as narrowing of the internal auditory meatus without nerve compression. Bilateral pale optic discs were noted on ophthalmological assessment (no clinical visual impairment) and mild bilateral low tone conductive hearing loss was detected on pure tone audiogram.

Osteopetrosis is a clinically and molecularly heterogeneous condition. The different subtypes share the hallmark of increased bone density resulting from abnormalities in osteoclast function or number. Reduced bone resorption leads to paradoxical increase in fragility and pathological fractures, encroachment of marrow space and variable degree of marrow failure, as well as bony expansion with compression of nerve foramina. Associated clinical features include hypocalcaemia, delayed dental eruption, and less commonly renal tubular acidosis, ectodermal dysplasia, immunodeficiency, retinal atrophy, sensorineural deafness, seizure and developmental delay.

The clinical spectrum is stratified into infantile (or malignant), intermediate and late-onset forms. Infantile form osteopetrosis presents during the first few months of life with pancytopenia, hepatosplenomegaly from extramedullary haematopoiesis, poor linear growth, macrocephaly and frontal bossing; neurological sequalae from nerve entrapment is significant and the prognosis is poor with fatality occurring during infancy. Late-onset form has its onset during late childhood or adolescence and may present as an incidental finding on X-rays, the autosomal dominant condition runs a benign course, but surveillance for the uncommon skeletal and neurological complications remain important. In our case, the diagnosis was made during early childhood (5 years old) with pancytopenia and extramedullary haematopoiesis, compatible with an intermediate form.

Bone marrow examination allows histological diagnosis and the differentiation between osteoclast-rich or osteoclast-poor subtypes, of which there is prognostic implication. Osteoclast-rich subtypes are mostly caused by defects in the osteoclast acidification machinery, whereas the rare osteoclast-poor subtypes are consequences of osteoclast differentiation failure. The osteoclast-poor form of autosomal recessive osteopetrosis is caused by mutations in either the *TNFSF11* or the *TNFRSF11A* genes, which encodes for the ligand and the receptor of the RANKL/RANK pathway. A distinction between *TNFSF11* and *TNFRSF11A* is important as patients with *TNFSF11* mutations do not respond to haematopoietic stem cell transplantation (HSCT).[1]

Responsible mutations can be delineated in approximately 70% of patients with osteopetrosis. GeneReview recommends if symptoms begin in early childhood (before the age of six), genetic testing should begin with *TCIRG1*, followed by *CLCN7*, *TNFSF11*, *TNFSF11A* and *OSTM1* (http://www.ncbi.nlm.nih.gov/books/NBK1127/). For our patient, we have decided to test the *TNFSF11* and *TNFRSF11A* genes first because of the osteoclast-poor appearance in the trephine biopsy and as discussed, the former mutation has been associated with suboptimal response to HSCT. Both mutations were not present in the child and he was worked up for matched-unrelated donor HSCT in view of the early onset of neurological complications.

Management of osteopetrosis is largely supportive. Use of medical treatment including Vitamin D, steroid and interferon-γ is controversial. HSCT is considered only in selected cases with intermediate or infantile forms due to procedure related morbidity and mortality plus its limited ability to reverse established disease complications.

### Reference

1. Sobacchi C, Frattini A, Guerrini MM, et al. Osteoclast-poor human osteopetrosis due to mutations in the gene encoding RANKL. Nat Genet 2007;39:960-2.

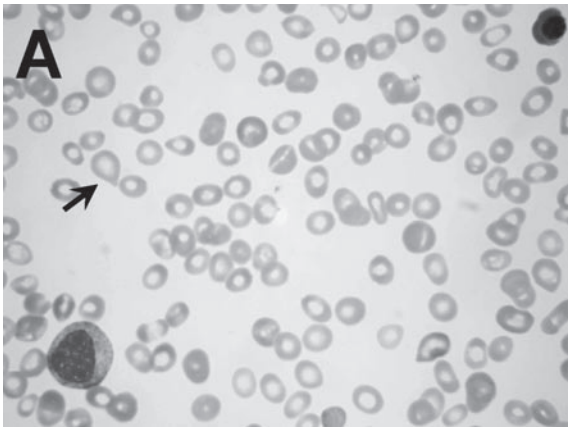


**Figure A** Leucoerythroblastic picture with polychromasia, and teardrop poikilocytes (arrow).

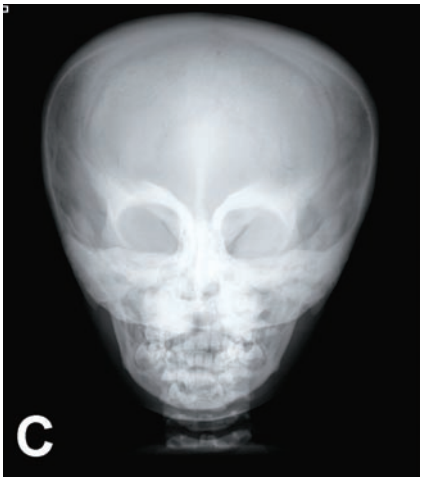


**Figure C** Thickened and sclerotic vault.

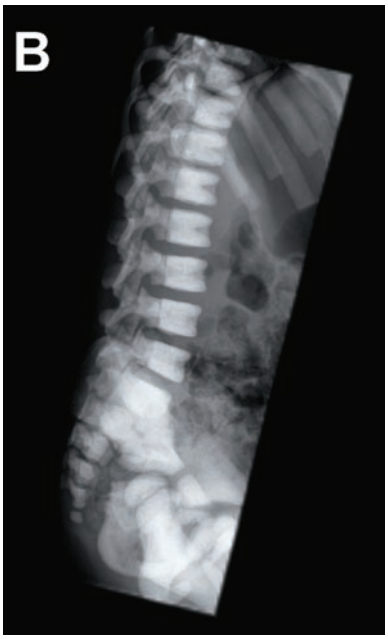


**Figure B** "Sandwich vertebrae".

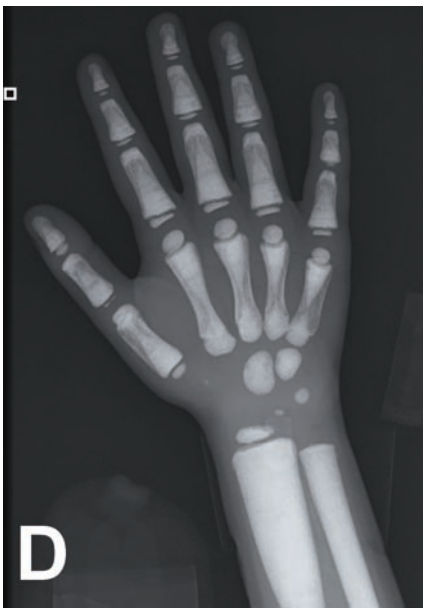


**Figure D** "Bone-in-bone" appearance of metacarpals.

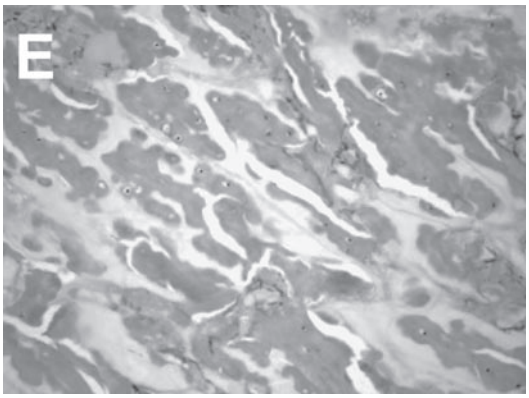


**Figure E** Trephine biopsy section showing irregularly thickened trabecular bone with complete encroachment of marrow spaces. Osteoclasts and osteoblasts are scarce.

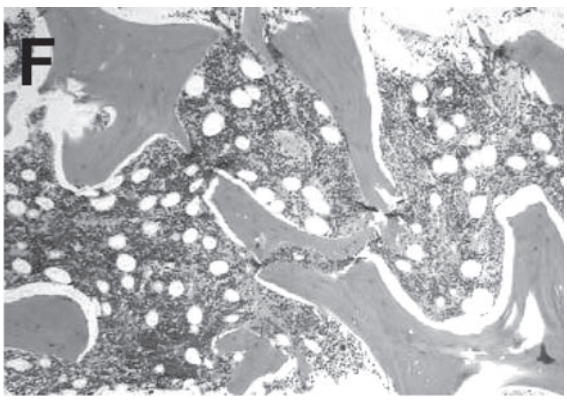


**Figure F** A normal trephine biopsy section showing normal haemopoietic elements in the intertrabecular spaces.