PLATELET REQUIREMENTS OVER FIFTEEN YEARS IN INFANTILE OSTEOPETROSIS.

Laura Pickett  
Department of Paediatrics,  
Ealing Hospital, Uxbridge Road,  
Middlesex UB1 3HW

Colin Michie*  
Department of Paediatrics,  
Ealing Hospital, Uxbridge Road,  
Middlesex UB1 3HW

ABSTRACT

Osteopetrosis, Albers-Schonberg or Marble Bone Disease refers to a group of rare genetic bone disorders with abnormal bone remodeling due to defective osteoclasts resulting in decreased bone resorption. The most serious form is malignant or infantile osteopetrosis which presents in early infancy and causes predisposition to fracture, bone marrow failure, developmental delay and cranial nerve damage. Mortality is usually high and hematological dysfunction occurring within the first three months of life from bone marrow failure is a poor prognostic indicator (1,2). A fifteen year old patient, diagnosed at five weeks of age with signs of hematological dysfunction, is presented. His clinical course illustrates several features that illuminate the role of various factors in the regulation of platelet counts.

CASE HISTORY

AI was born at term by normal vaginal delivery following an uneventful pregnancy, the second child of consanguineous Pakistani parents. He presented to hospital at the age of five weeks with suspected sepsis; he had craniofacial dysmorphism including frontal bossing and persistent thrombocytopenia with levels of 10^9l-1. The chest and pelvic X-rays revealed hyper-dense bone and a bone marrow aspirate showed abnormal hyperplastic leukemoid marrow appearance. A genetic diagnosis by PCR revealed a mutation in the TCIRG1 proton pump confirming the diagnosis of osteopetrosis.

Haploidentical peripheral blood stem cell transplantation and a bone marrow transplant were attempted in his first year of life. These resulted in graft rejection after three months. Following this the patient was managed supportively with regular transfusions of platelets, red cells and immunoglobulins. His disordered bone growth resulted in craniosynostosis, obliteration of facial sinuses, and pathological fractures of his right humerus.

* Communicating Author: colin.michie@eht.nhs.uk
and both femurs. He required gastrostomy feeds and speech and language therapy related to his developmental delay. AI developed splenomegaly in the first year of life; by the second year the liver became enlarged too, clinically. He was treated with regular antacids, an oral iron chelating agent, daily folic acid, penicillin V and 5mg prednisolone. He was found to have some paravertebral masses on ultrasound, thought to represent extramedullary haematopoietic tissue. During his monitoring his total white cell count, neutrophil and lymphocyte counts remained within normal limits. He did not develop red cell or platelet alloantibodies despite large numbers of blood product transfusions.

The results of the monthly platelet counts and timings of transfusions of platelets provided are documented below (see graph). Platelet transfusions were provided on a symptomatic basis, that is, easy bruising. The bruising seen by his family and staff was usually on his forearms and legs; on some occasions he had rounded bruises on the upper arms from being picked up. The bruises showed a petechial pattern on occasions. He did not show bruising within the ‘safe triangle’ of the side of the head and neck. This is an area in which accidental bruising is thought to be very rare – a useful marker from the perspective of child protection. At no point has there been an episode of bleeding into the brain, eyes, gut or genitourinary system. AI has had 5 admissions to Hospital for infections: he has suffered little from common childhood viral infections. Red cell transfusion records were less common than those for platelets.

When he was 4 years old a decline in platelet count corresponded with an attempt to decrease the patient’s oral steroid dosage; the steroid dose was subsequently increased. Between mid 2001 and throughout most of 2002, in late 2006 and throughout most of 2007 transfusions were not required. In early 2004 AI required increased number of transfusions, but no cause was identified. There did not seem to be any link to infection, administration of vaccines, foreign travel, admission for bony trauma or seasonality. In 2006 he presented with bleeding from both ears following an episode of head butting; a CT scan showed evidence of a recent parietal contusion but no intracranial haemorrhage. In early 2008 a severe episode of osteomyelitis following a femur fracture corresponded with an increased need for transfusions. See Graph 1.

**DISCUSSION**

Bone marrow provides critical microenvironments for haematopoietic stem cells. This case represents a valuable insight in terms of maintaining circulating cell numbers in the face of a sclerotic bone disorder that removes such niches from infancy and transfers these functions to other anatomical sites. Little is known of the regulation of this process.
There are three distinct phenotypes of osteopetrosis: infantile malignant autosomal recessive, intermediate autosomal recessive, and adult benign autosomal dominant (3). The most severe is the infantile malignant form, as in the case described here. Three defective genes involved in the acidification of the resorptive lacunae of osteoclasts have been implicated in malignant osteopetrosis: CAII carbonic anhydrase (4), CLCN7 chloride channel (5), and TCIRG1 proton pump (6). Mutations in the latter, as demonstrated in this patient, comprise approximately 60% of cases and lead to the most severe phenotype with presentation in infancy, frontal bossing, hepatosplenomegally, and death usually within the first decade of life (1,2). Murine models of osteopetrosis suggest that with time the animals can adjust to loss of such bone microenvironments. In patients with malignant osteopetrosis the majority of extramedullary hematopoiesis occurs in the liver and spleen with some occurring in the skull base, calvarium (7) and ectopic sites in the thorax and abdomen (8,9,10).

The case demonstrates that extramedullary haematopoiesis in this condition can generate a low level of erythropoiesis and reasonable neutrophil counts, but is insufficient to maintain adequate platelet counts. Why might this be the case? Platelets are two to three micrometre diameter cell fragments derived from megakaryocytes; they have a life span in the circulation of five to nine days and play roles in haemostasis and growth factor production (11). Haematopoietic stem cells in the bone marrow produce megakaryoblasts, precursors to megakaryocytes. After multiple cycles of megakaryoblastic nuclear endoreduplication, a process where DNA replication occurs without cytoplasmic cell division (12), a mature megakaryocyte is formed. Two methods for platelet generation have been proposed: long megakaryocyte processes protruding into marrow sinusoids might produce platelets (13,14), or megakaryocytes themselves might travel to the lung capillaries and release platelets there (15). One mature megakaryocyte can give rise to between 1000 and 5000 platelets (16). The primary cytokine responsible for platelet formation is thrombopoietin (TPO) (17,18,19) which stimulates proliferation and differentiation of megakaryocyte precursors (20), promotes megakaryocyte maturation (17,18), and stimulates the release of platelets from megakaryocytes (21). The normal range for human platelet levels is 150,000 to 450,000 per microlitre of blood but this can vary widely between individuals. Platelet levels below 50,000 result in increased risk of bruising and bleeding.

AI had platelet levels below 50,000 for most of his life yet required relatively few transfusions; they were only being administered symptomatically. His requirement for red cell transfusions was low; he developed remarkably effective extramedullary haematopoiesis that was only incompetent with respect to platelet generation.
CONCLUSIONS

The case history of an adolescent with infantile osteopetrosis demonstrates the success of extramedullary haematopoiesis in the production of many cell types at relatively normal levels, but not platelets. From the perspective of child protection the condition is salutary: despite a fragile skeleton and low platelets AI never developed bruises in the ‘safe’ triangle of head and neck and never bled into the retina or brain.

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REFERENCES


