

Transient abnormal myelopoiesis in an infant with Down syndrome

Emily Payne¹, Ahmed Salamt² and Philip Connor^{1*}

¹Department of Hematology, Children's Hospital for Wales, Heath Park, UK; ²Department of Hematology, Singleton Hospital, ABM University NHS Trust, Sketty, UK

Received: 8 September 2009; Accepted in revised form: 21 November 2009; Published: 13 January 2010

Case presentation

A three-week-old boy with Down syndrome presented with poor feeding and jaundice. He had been born at term by normal delivery at home. The pregnancy had been uneventful and the mother had declined antenatal testing so the diagnosis of Down syndrome was made in the postnatal period. The infant required oxygen at birth and was admitted to the neonatal unit for a few days after birth. He started to become jaundiced after discharge. There was no family history of note and the infant has three siblings who are healthy. The mother is Rh D positive.

On examination the infant was jaundiced, with neither hepatosplenomegaly, nor signs of sepsis but had hypotonia typical of Down syndrome. Investigations revealed unconjugated jaundice with a negative direct antiglobulin test. A full blood count showed thrombocytopenia with a platelet count of $65 \times 10^9/L$, a white cell count of $8.6 \times 10^9/L$, neutrophil count of $1.9 \times 10^9/L$ and haemoglobin level of 18.0 g/dL. Blast cells of medium to large size with cytoplasmic blebs were found on the blood film (see Fig. 1). Immunophenotyping showed the blasts to have myeloid markers with expression of CD41 and CD61.

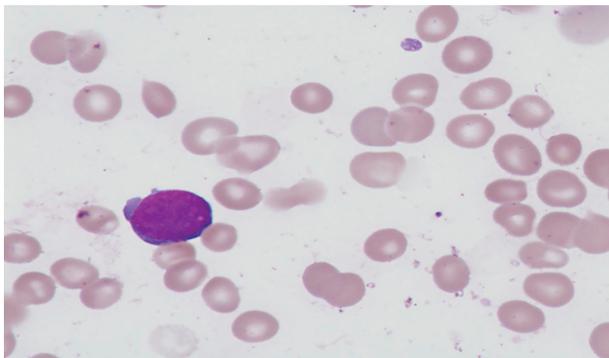


Fig. 1. Photomicrograph of a typical TAM blast cell seen on a blood film (600 × oil immersion objective).

The infant was treated with phototherapy and the jaundice improved. He was followed up closely with weekly full blood counts for two months.

Diagnosis

Transient abnormal myelopoiesis (ICD-O 9898/1).

He was reviewed in clinic after three months when he was found to be well and gaining weight. His full blood count showed the previously documented thrombopenia had normalised but neutropenia had persisted: haemoglobin 11.5 g/dL, white cell count $5.4 \times 10^9/L$, platelets $334 \times 10^9/L$ and neutrophils $1.09 \times 10^9/L$. Vacuolated neutrophils, reactive lymphocytes and the occasional primitive cell were seen on blood film reflective of a reactive process. Within a further two months and at an age of six months his full blood count had normalised completely confirming that the diagnosis had been transient abnormal myelopoiesis (TAM). He continues to have monthly full blood counts as 70% of acute myeloid leukaemia (AML) cases following TAM develop some form of cytopenia prior to developing an increasing blast percentage.

Discussion

TAM is the clonal proliferation of myeloid blast cells which affects an estimated 5–10% of infants with Down syndrome and trisomy 21 mosaicism (1). The majorities of infants with TAM are asymptomatic and picked up incidentally on routine testing. Most cases of TAM resolve over the first few months of life, but 13–33% may go on to develop AML within the first four years of life.

Neonates with Down syndrome are unique in having a predisposition to transient abnormal myelopoiesis (2). One of the reasons for this is thought to be that trisomy 21 affects foetal liver haematopoiesis causing an increase in the megakaryocyte-erythroid progenitor frequency with common myeloid progenitors and a reduction in the granulocyte-monocyte progenitors. Increased clonogenicity affecting megakaryocyte-erythroid progenitors,

granulocyte–monocytes and colony-forming unit-granulocytes has also been found (3). GATA-1 mutations, a transcription factor mutation integral to the normal development of erythroid, megakaryocytic and basophilic cell lines, have been associated with TAM and AML in Down syndrome (4). As such, TAM and myeloid leukaemia of Down syndrome provides an excellent model for leukaemogenesis (5).

TAM is difficult to diagnose and is not easily distinguished from AML. Microscopically, TAM is seen as an increase in the number of blasts on peripheral blood film with thrombocytopenia or other cytopenias. There may be fewer blasts in the marrow than peripheral blood.

Five-year survival after TAM is 85% and event-free survival 63% (1). The typical clinic picture of a patient requiring treatment is one of an unwell infant on intensive care with an oxygen or inotrope requirement or serious bleed. Often they have hepatomegaly. Factors associated with early death in TAM include a high white cell count, increased liver enzymes, failure to normalise the blood count, ascites, preterm delivery, bleeding diatheses and failure of spontaneous remission (1).

These events can occur in utero and be a cause of foetal death. Treatment with low-dose cytarabine in TAM patients with a high white cell count, thrombocytopenia or liver dysfunction has been found to have a favourable effect on five-year event-free survival (1). The dose chosen is usually 1–2 mg/kg intravenous or subcutaneous daily for 3–7 days (1). The diagnosis of TAM has prognostic importance as AML patients with a history

of TAM have a better five-year event-free survival than those without (1).

Conflict of interest and funding

The authors have not received any funding or benefits from industry to conduct this study.

References

1. Klusmann JH, Creutzig U, Zimmermann M, Dworzak M, Jorch N, Langebrake C, et al. Treatment and prognostic impact of transient leukaemia in neonates with Down syndrome. *Blood* 2008; 111: 2991–8.
2. Webb D, Roberts I, Vyas P. Haematology of Down syndrome. *Arch Dis Child Fetal Neonatal Ed.* 2007; 92: F503–7.
3. Tunstall-Pedoe O, Roy A, Karadimitris A, de la Fuente J, Fisk NM, Bennett P, et al. Abnormalities in the myeloid progenitor compartment in Down syndrome fetal liver precede acquisition of GATA1 mutations. *Blood* 2008; 112: 4507–11.
4. Ahmed M, Sternberg A, Hall G, Thomas A, Smith O, O'Marcaigh A, et al. Natural history of GATA1 mutations in Down syndrome. *Blood* 2004; 103: 2480–9.
5. Vyas P, Roberts I. Down myeloid disorders: a paradigm for childhood preleukaemia and leukaemia and insights into normal megakaryopoiesis. *Early Hum Dev.* 2006; 82: 767–73.

*Philip Connor

Department of Hematology
Children's Hospital for Wales
Heath Park, UK
Email: Philip.connor@cardiffandvale.wales.nhs.uk