

CASE REPORT

Transient abnormal myelopoiesis in newborns with Down syndrome

AL Zarina *MMed (Paeds), MSc (Medical Genetics)*, A Hamidah *MMed (Paeds)*, Yong SC *MBBCh, MRCP*, J Rohana *MMed (Paeds)*, NH Hamidah* *MBBCh, DCP*, Azma RZ* *MBBS (Mal), MPath (UKM)*, NY Boo *FRCP*, R Jamal *MRCP, PhD*

*Departments of Paediatrics and *Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*

Abstract

Transient abnormal myelopoiesis (TAM) is a haematological phenomenon commonly seen in newborns with Down syndrome. Although the majority show spontaneous resolution, this condition should not be dismissed too readily as there have been associated fatalities. Furthermore, even for those who do show spontaneous resolution, a significant percentage will develop acute megakaryoblastic leukaemia within the next few years of life. We report a series of four patients with TAM who presented with hepatosplenomegaly and leucocytosis detected on preliminary investigations.

Key words: transient abnormal myelopoiesis, Down syndrome

INTRODUCTION

Down syndrome (DS) is a common chromosomal disorder which causes mental retardation. There are many complications which may be associated with Down syndrome: congenital heart disease, gastrointestinal malformations, endocrine and also haematological disorders amongst others. These complications may be evident either at birth or may develop at a later age. It has been shown that the risk of developing acute leukaemia in children with Down syndrome is 1 in 95 within the first 10 years of life.¹ Of these, acute megakaryoblastic leukaemia (AMKL) is the commonest.

Transient abnormal myelopoiesis occurs in up to 10% of newborn infants with Down syndrome.² Many studies have shown a link between transient abnormal myelopoiesis (TAM) and AMKL. TAM is in fact a form of transient leukaemia as the cells of TAM are proliferating from a single cell i.e. monoclonal. Most cases of TAM resolve spontaneously; however, up to 20% will develop AMKL later.²

CASE REPORTS

Patient 1

This female infant was delivered at term with a birth weight of 3400 grams. Clinically

she had features of Down syndrome with hepatosplenomegaly of 7 and 3 centimetres respectively. She had progressive respiratory distress requiring nasal continuous positive airway pressure (CPAP). Her first chest radiograph showed cardiomegaly with pulmonary plethora. An echocardiogram confirmed a diagnosis of a complex cyanotic heart disease: atrioventricular septal defect (AVSD), patent ductus arteriosus (PDA) with total anomalous pulmonary venous drainage (TAPVD). Abdominal ultrasonography showed right diaphragmatic paresis.

Full blood count on day 1 of life revealed leucocytosis ($45 \times 10^9/L$) and the blood film showed a leucoerythroblastic picture with 41% blasts. Her uric acid level was normal but lactate dehydrogenase (LDH) was elevated at 2175 U/L. Allopurinol and alkalinized diuresis were instituted. A bone marrow examination performed on day 6 of life showed 9% blasts; a diagnosis of transient abnormal myelopoiesis was made. Supportive management (i.e. intravenous hydration and alkalinised diuresis) was continued and the total white cell count gradually declined to $8.1 \times 10^9/L$ by day 19 of life. Unfortunately the infant died due to methicillin-resistant staphylococcus aureus (MRSA) septicaemia at day 32 of life.

Patient 2

This male infant who was delivered at 40 weeks gestation with a birth weight of 1490 grams had hepatosplenomegaly at birth measuring 7 and 3 centimetres respectively. He was initially treated for congenital pneumonia requiring nasal CPAP support. Routine echocardiography showed a small PDA with minimal pericardial effusion. The initial full blood picture on day 1 showed hyperleucocytosis ($199 \times 10^9/L$) with the presence of blast cells. He was started on Allopurinol and his intravenous fluids were increased to double his normal requirement. Sodium bicarbonate infusion was also commenced to alkalinize his urine with close monitoring of his blood electrolytes. The parents refused bone marrow examination.

He was supportively treated for nosocomial sepsis and necrotising enterocolitis. His white cell count gradually normalized at day 14 of life to $9 \times 10^9/L$. Unfortunately, his condition deteriorated on day 23 of life when he developed progressive ascites with enlarging hepatosplenomegaly. He became pancytopenic and had disseminated intravascular coagulopathy; blood culture grew *Klebsiella* species. He was treated with intravenous Imipenem and regular transfusions of blood products (packed cells, platelet concentrates, fresh frozen plasma and cryoprecipitate). His respiratory support was subsequently changed to high frequency oscillatory ventilation (HFOV). Unfortunately, despite all the supportive management, he succumbed at day 45 of life.

Patient 3

The third infant was delivered at 35 weeks of gestation. She developed respiratory distress at birth requiring HFOV support. Clinically there was no heart murmur; she had hepatosplenomegaly of 6 and 2 centimetres respectively. Echocardiography at 4 hours of life showed a normal intracardiac anatomy but there was bi-directional shunting at the ductus arteriosus. Her oxygen index was elevated; a diagnosis of persistent pulmonary hypertension of the newborn (PPHN) was made. She was started on inhaled nitric oxide and inotropic support. The first full blood count showed hyperleucocytosis ($270 \times 10^9/L$) with the presence of 79% blasts; both the uric acid and LDH were also elevated (441 and 1325 U/L). Allopurinol was commenced orally and the intravenous fluids were doubled her normal requirement. Sodium bicarbonate infusion

was also started. Unfortunately, she developed persistent hypotension despite triple inotropic support; her PPHN could not be reverted. She developed acute renal failure and succumbed at day 4 of life.

Patient 4

This male infant was delivered at term with a birth weight of 3.4 kg. He developed respiratory distress at 90 minutes of life and was subsequently diagnosed to have tracheo-oesophageal fistula (TOF) type III; he also had patent ductus arteriosus with atrial septal defect. Surgical repair for the TOF was done at day 2 of life.

However, on day 7 of life, leucocytosis was detected on routine blood investigations, with a white blood cell count (WBC) of $89 \times 10^9/L$ with 41% blast cells. There was also hepatosplenomegaly (3 and 2 cm respectively). Bone marrow examination at day 8 showed features suggestive of transient abnormal myelopoiesis. Unfortunately, he developed tumour lysis syndrome, which was managed supportively: allopurinol, intravenous sodium bicarbonate, hydration fluids and diuretics were administered. This event was complicated by *Klebsiella* septicaemia and he required ventilatory support. Peripheral blood film on day 14 showed presence of 78% blast cells (Fig. 1). A repeat bone marrow examination at day 16 of life showed features of transient abnormal myelopoiesis (Fig. 2), whereas immunophenotyping showed expression of CD45, HLA-DR, CD34, CD33 and CD61 (Fig. 3). By day 39, his WBC count had normalised to $16.4 \times 10^9/L$, and he was discharged by day 46. Unfortunately at 17 months of life he presented with pallor, fever and hepatosplenomegaly. Bone marrow examination confirmed that he had developed acute myeloid leukaemia (M7).

DISCUSSION

Transient abnormal myelopoiesis (TAM) or transient leukaemia is seen in up to 10% of newborns with Down syndrome.² If in-utero cases are also taken into account, then the incidence would increase to approximately 20%.

In classic TAM, there are usually no overt clinical features although hepatosplenomegaly (as seen in all our patients) and vesicopustular lesions have been reported. The presence of blast cells (or leukaemic cells) is usually detected

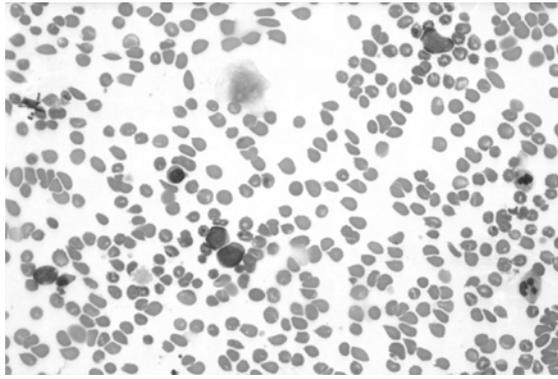


FIG. 1: Peripheral blood film of patient 4 at day 14 of life showing presence of blast cells (78%) (Wright stain x 40).

on routine blood investigations; an interesting feature is that the basophil count is relatively high – a level as high as $56 \times 10^9/L$ has been reported. The presence of dysplastic nucleated red cells, megathrombocytes and megakaryocyte fragments has also been observed. Generally, patients with classic TAM remain well and the leukaemic cells gradually decline and disappear totally by the second to third month of life. In our first two patients, blast cells were detected on the first day of life but declined within the first three weeks of life itself. The haemoglobin and platelet counts are normal in most cases of TAM, which was similarly seen in all our patients.

Although the majority of patients with TAM classically show spontaneous resolution, the clinician should still be aware that up to 19% are complicated by life – threatening complications.¹ This group of patients may present with either progressive hepatic disease or cardiopulmonary disease. In the former,

there is progressive obstructive jaundice leading to terminal hepatic failure. Histological examination shows evidence of hepatic fibrosis with megakaryoblastic infiltration. In TAM complicated by cardiopulmonary disease, patients present with hydropic – like features. There is direct infiltration of leukaemic cells into the cardiac muscle with resultant pleural and pericardial effusions. In such cases, low dose chemotherapy (using cytosine arabinoside) may be curative.³ Although the first three patients in our series resulted in mortality, these were attributed to fulminant septicaemia. Furthermore, none of them had features of either obstructive liver disease or cardiopulmonary disease. Patients 1, 2 and 4 also had congenital (structural) heart disease but there were no hydropic features such as generalised oedema, significant pleural or pericardial effusions at initial presentation. In view of this, they would still be grouped as classic TAM.

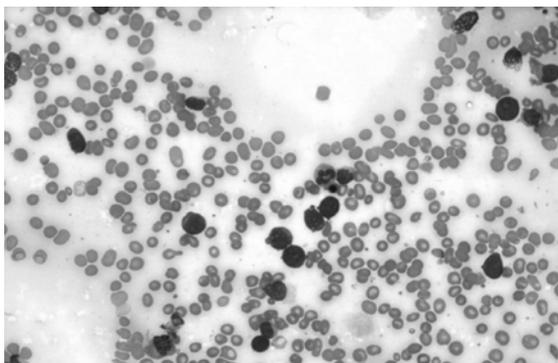


FIG. 2: Bone marrow aspiration smear of the patient at day 16 of life showing presence of 40 – 50% blasts. Morphologically the blasts are heterogenous in size with basophilic cytoplasmic blebs and the nuclei have prominent nucleoli. (MGG stain x 40)

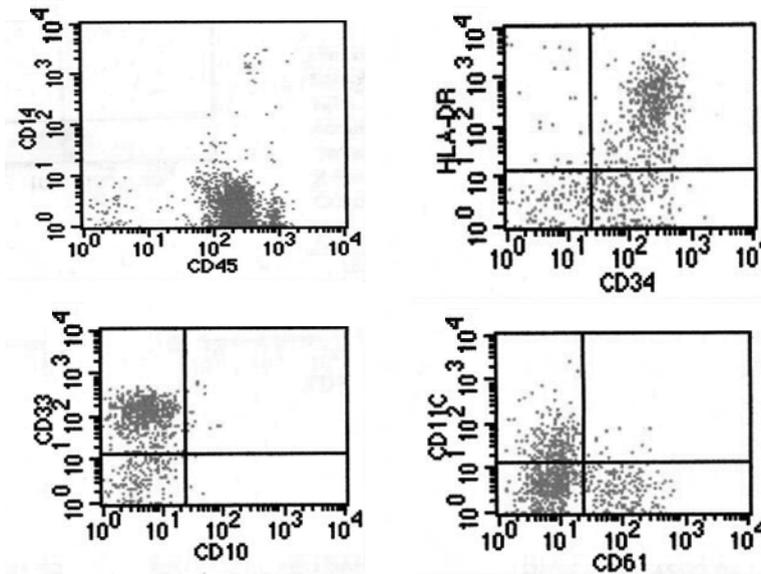


FIG. 3: Immunophenotyping done at day 16 of life showed the gated mononuclear cells expressed CD45, HLA-DR, CD 34, CD 33 and CD61. Findings are consistent with acute myeloid leukaemia (M7).

Bone marrow examination usually reveals certain unique features: cellular marrow with a large number of dysplastic megakaryocytes, which is similar to the myelodysplasia observed in the early stages of acute megakaryoblastic leukaemia. Blasts are present and their numbers are similar to, and directly related to, the percentage of blasts in the peripheral blood. This is unlike other forms of leukaemia where the marrow is virtually replaced by leukaemic cells.

All our patients were managed supportively in terms of the haematological problem. Allopurinol, adequate hydration, diuresis and alkalinisation were important aspects of management as these patients had the potential to develop tumour lysis syndrome. In patient 3, although there was hypotension, the presence of hyperleucocytosis may have contributed to the development of acute renal failure. In cases where WBC count exceeds $200 \times 10^9/L$, leukapheresis or exchange transfusion needs to be considered; however, the patient's clinical status should first be stabilised.

As mentioned previously, although most cases of TAM are self-limiting, it has been reported that up to 20% of such cases will develop acute megakaryoblastic leukaemia (AMKL) within the first four years of life. This is probably not surprising as the ultrastructure and surface antigen expression (CD 41 and CD 61 namely) indicate that the leukaemic cells of

TAM have the properties of a megakaryocytic precursor cell or megakaryoblast.² In TAM however, the cells have more megakaryocytic differentiation.² There was expression of CD 61 in the immunophenotyping of our last patient (Fig. 3) who subsequently developed acute megakaryoblastic leukaemia (AMKL) at the age of 17 months; morphologically, he had the M7 subtype.

There have been continuous debates regarding 'labelling' TAM as a form of leukaemia in view of the frequent spontaneous resolution without any definitive treatment. Several researchers have however shown that the leukaemic cells of TAM are monoclonal which is consistent with a leukaemic process.² These leukaemic cells also have the potential of forming cells of the basophilic series. Occasionally, these leukaemic cells have clonal cytogenetic abnormalities; acquired chromosome 21 anomalies such as tetrasomy 21, translocation (21;21) and isochromosome 21 are the most common.^{2,4} An interesting point to note here are that these chromosomal abnormalities and leukaemic cells disappear at the same time. In addition to this, infiltration into non-haematopoietic tissues (including skin), is further supportive evidence that TAM is indeed a form of leukaemia.

Although TAM occurs almost exclusively in neonates with Down syndrome, there are case reports in which phenotypically normal children have TAM with trisomy 21 in the

leukaemic cells but not in the skin fibroblasts or phytohaemagglutinin stimulated lymphocytes.^{2,4} Other complex chromosomal rearrangements (deletions and inversions) involving chromosome 21 have also been reported. Based on these findings, speculations have been made that the region 21q11 may contain a gene important in the development of TAM. Hitzler *et al* have discovered GATA – 1 mutations in the cells of patients with TAM; GATA – 1 is a transcription factor, which is necessary for normal megakaryocytopoiesis.⁵

Transient abnormal myelopoeisis is a unique form of leukaemia that occurs predominantly in infants with Down syndrome and in cells that are trisomic for chromosome 21. Although the majority resolves spontaneously, there is an inherent risk that AMKL may develop later. Unfortunately, there are no definite clinical or haematological features that will differentiate those who will develop AMKL; in view of this, close clinical surveillance should be performed for the first few years of life.

REFERENCES

1. Lanzkowsky P, editor. Manual of Pediatric Hematology and Oncology. 3rd ed. Academic Press, 2000.
2. Zipursky A. Transient Leukaemia – A benign form of leukaemia in newborn infants with Trisomy 21. Br J Haematology 2003; 120: 930 – 8.
3. Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's Syndrome. Br J Haematology 2000; 110: 512 – 24.
4. Kempski HM, Craze JL, Chessells JM *et al*. Cryptic deletions and inversions of chromosome 21 in a phenotypically normal infant with transient abnormal myelopoeisis: A molecular cytogenetic study. Br J Haematology 1998; 103: 473 – 79.
5. Hitzler JK. GATA 1 – A player in normal and leukaemic megakaryopoiesis. Ped Research 2002; 52 (6): 831.