Down Syndrome with Different Hematological Manifestations: A Short Series of 3 Cases with Review of Literature

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Abstract Children with Down syndrome (DS) present with a spectrum of hematolymphoid malignancies ranging from transient myeloproliferative disorder (TMD) which regress spontaneously to frank acute leukemia of both myeloid and lymphoid lineage. Here we present a series of three cases with different manifestation in DS. Three cases of DS presented with TMD, acute myeloid leukemia (AML–M2) and acute megakaryoblastic leukemia (AMKL), respectively. This case series displays the spectrum of hematological manifestations in children with DS. Although TMD and AMKL are strongly associated with DS, other AML subtypes can also be seen in such patients.

Keywords Down syndrome · Transient myeloproliferative disorder · Acute myeloid leukemia · Acute megakaryoblastic leukemia

Introduction

Patients with Down syndrome (DS) have a higher risk (10- to 20-fold) of developing leukemia [1, 2]. In the WHO classification of tumours of haematopoietic and lymphoid tissues 2008, myeloid proliferations related to DS has been incorporated as a distinct entity [3]. A unique syndrome occurs only in newborn infants with DS referred to as transient myeloproliferative disorder (TMD), transient abnormal myelopoiesis (TAM), or transient leukemia (TL). In addition, children with DS are also at increased risk for acute megakaryoblastic leukemia (AMKL) and acute lymphoblastic leukemia (ALL) in the first 4 years of life [2].

We report a short series of 3 cases with different hematological manifestations in children with DS diagnosed over a period of 6 months.

Case 1

A 2.5 kg male baby was born at term to a 28 year old mother of a consanguineous marriage by normal spontaneous vaginal delivery after an uncomplicated gestation. There was no history of drug intake or exposure to radiation during the antenatal period. There was history of birth asphyxia and child was admitted in neonatal intensive care unit. Physical examination revealed features of DS (anti-mongoloid slant, short stubby fingers, hypotonia). There was no evidence of sepsis. On day 2 of life, routine blood investigation was done. The Hb was 178 g/l and platelet count (PC) was $271 \times 10^9/l$. The TLC was $18 \times 10^9/l$ with 7% blasts, 2% myelocytes, 3% metamyelocytes, 6% band forms, 64% neutrophils, 17% lymphocytes, 1% eosinophils (Fig. 1a). Some of the blasts showed cytoplasmic blebs (Fig. 1a, inset a). On cytochemistry, these blasts were positive for Myeloperoxidase (MPO) (Fig. 1a, inset b) and on immunocytochemistry (ICC), blasts were positive for CD 34 but negative for CD 61. Bone marrow aspirate (BMA) was deferred and the child was kept under close monitoring and advised repeat peripheral smear (PS) after 2 week. On day 14, repeat Hb was 130 g/l and PC was $281 \times 10^9/l$. The TLC had decreased to $9 \times 10^9/l$ with 1% blast, 2% myelocytes, 4% metamyelocytes, 44% neutrophils, 45% lymphocytes, 4% monocytes. On follow-up after 1 month, TLC had normalized with no circulating blast in the periphery (Fig. 1b). The final impression of TMD associated with DS in spontaneous remission was made.

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Fig. 1 **a** Case 1—PS with leucocytosis and 7% blasts at presentation (inset: **a**—blast showing cytoplasmic blebs; **b**—blast with MPO positivity) (Leishmann stain, $\times 400$). **b** Case 1—follow-up PS after 1 month shows normalization of total count with no blast (Leishmann stain, $\times 400$). **c** Case 2—BMA with many myeloblasts (Leishmann stain, $\times 1000$). **d** Case 2—PS showing myeloblasts along with

increased basophils (Leishmann stain, $\times 1000$). **e** Case 3—BMA showing increased myeloblasts (inset **c**—Blast with PAS positivity) **f** Case 3—BMA showing varied morphology of myeloblasts with cytoplasmic blebbing (inset: **d**—blast with CD 61 immunostain positivity) (Leishmann stain, $\times 1000$)

Case 2

A 1½ year old female child with features of DS presented with fever and progressive weakness of 10 days duration. Physical examination revealed severe pallor, moderate hepatosplenomegaly but no lymphadenopathy. The Hb was 29 g/l and PC was $22 \times 10^9/l$. PS showed normocytic

normochromic red cells with polychromatophils, macrocytes and nucleated RBC-28/100 WBC, many of which showed dyserythropoiesis. The TLC was $33 \times 10^9/l$ with 65% blasts, 1% myelocyte, 2% metamyelocytes, 9% neutrophils, 6% lymphocytes, 4% eosinophils and 13% basophils (Fig. 1c, d). BMA showed suppressed megaloblastic erythropoiesis and megakaryopoiesis and myeloid hyperplasia

with increase in blasts comprising 71% of marrow cells along with myeloid maturation. The blasts were heterogeneous; some had granular cytoplasm though no distinct Auer rods were seen (Fig. 1c). Some blasts showed cytoplasmic blebs. Basophils were increased (6%). On cytochemistry, blasts were MPO positive and periodic acid Schiff (PAS) negative. ICC was performed – blasts were positive for CD 34 and negative for TdT, CD 3, CD 10, CD 20, CD 61, and CD 68. The final diagnosis of acute myeloid leukemia with maturation (AML-M2) with basophilia was given.

Case 3

A 2 year old male child presented with fever, subcutaneous bleeds and ecchymosis of 4 days duration. Physical examination revealed pallor, mild hepatosplenomegaly and significant cervical and axillary lymphadenopathy and features of DS. The hemoglobin (Hb) was 81 g/l and PC was $12 \times 10^9/l$. The total leucocyte count (TLC) was $40 \times 10^9/l$ with 10% neutrophils, 4% lymphocytes, 2% eosinophils and 84% blasts. BMA showed 88% blasts. The blasts were heterogeneous (Fig. 1e) and many showed cytoplasmic blebs, reminiscent of megakaryoblast (Fig. 1f). MPO was positive and in addition, occasional blasts showed PAS positivity (Fig. 1e, inset c). On ICC – blasts showed positivity for CD 61 (Fig. 1f, inset d), MPO and were negative for TdT, CD 3, CD 10, CD 20, CD 68. The final diagnosis of AMKL was given.

Discussion

DS results from trisomy 21 and occurs in approximately 1 in 1,000 birth [4]. The first report of leukemia in DS patient occurred in 1930 and subsequent contemporary studies indicate that patients with DS have a 10- to 20-fold higher relative risk for leukemia, with cumulative risk of 2% by age 5 and 2.7% by age 30. In addition to the higher frequency, leukemia in DS patient also differs in their clinical features, timing of occurrences, and response to therapy. [1] In the WHO classification of tumours of haematopoietic and lymphoid tissues 2008, myeloid proliferations related to DS has been incorporated as a distinct entity [3].

Approximately 10% of newborn infants with DS develop a form of megakaryoblastic leukemia which usually disappears spontaneously during the first few months of life known as TMD or TL. It is characterized by the large number of megakaryoblasts in the peripheral blood, variable thrombocytopenia and in a minority of cases, by a lethal course with hydrops fetalis or progressive hepatic fibrosis. Recent evidence of the clonal nature of the disease favors the

hypothesis that TMD represents a very special form of leukemia. Studies have shown that 25% of cases that had spontaneous remission developed AMKL in the first 4 years of life, which, if not treated, had fatal outcome [5, 6]. The reason for the complete and spontaneous resolution is not known [7]. Children Oncology Group (COG) study POG-9481 – a multi-institutional prospective study had extensively investigated the natural history of TMD in newborn with DS or trisomy 21 mosaicism. Candidate genes for leukemogenic potential that are expressed on chromosome 21 include the FPDMM gene (cause of the autosomal dominant familial platelet disorder), AML 1 gene (associated with AML-M2), interferon alpha receptor (INFA), CRF 2-4 (cytokine receptor family 2-4) and phosphoribosylglycinamide formyltransferase. However, whether this is simply a result of increased gene dosage or a result of disomic homozygosity remains to be determined [2].

There is approximately 150-fold increase in AML in DS children less than 5 years of age; 70% of the cases of AML in DS children less than 4 years of age are AMKL in contrast to the 3–6% incidence of this form of leukemia in non-DS children [3]. A few case reports of congenital leukemia in the newborn or in the immediate neonatal period occurring in DS are reported and strict diagnostic criteria have been proposed [8, 9]. There are some minor hematologic and cytogenetic differences between TMD and AML in DS. TMD tends to manifest with normal hematopoiesis and PC and usually has only the constitutional trisomy 21 whereas AML generally exhibit cytopenia and show additional complex cytogenetic abnormalities [10]. In our case series, platelets were normal in TMD and decreased in both cases of AML.

Karandikar et al. [10] analysed the immunophenotypic expression by using multiparameter flow cytometry in TMD and AML in DS. Their study indicate that there are characteristic similarities between the myeloid blast populations of AML and TMD in DS which includes CD 45+, CD 38+, CD 33+, CD 36+, CD 41+, CD 61+, CD 34+, CD 14–, CD 64– indicating megakaryocytic/erythroid differentiation [10]. In our series of 3 cases immunophenotyping by ICC did not show positivity for CD 61 in case 1, but based on close follow-up with disappearance of blast we labeled that case as TMD in spontaneous remission. However, ICC showed CD 61 positivity in case 3 indicating megakaryocytic differentiation.

GATA 1 is a phosphorylated, double zinc finger, DNA-binding transcription factor encoded on the X-chromosome. GATA1 is a key regulator of megakaryocyte, erythroid, eosinophil, and mast cell differentiation. It has central role in regulating megakaryoblast numbers and ensuring normal megakaryocyte and platelets differentiation. Both in TMD and in DS AMKL acquired somatic mutations in one copy

of GATA1 were demonstrated mainly in the first coding exon, exon 2 [11].

Event free survival rates for DS patients with AMKL ranges from 80 to 100% in comparison with <30% for non-DS children with AMKL. They are especially sensitive to cytarabine (ARA-C), possibly due to the effect of the GATA1 mutations and trisomy 21 on the levels of cytarabine-metabolizing enzymes [12]. We lost case 2 and 3 to follow-up, hence response to chemotherapy could not be commented upon.

Although DS ALL is not a unique disease entity as are DS AMKL and TMD, it differs importantly from non-DS ALL. The incidence of DS ALL follows the same age peak as in non-DS, with the exception that almost no cases occur in infants <1 year of age. T-cell and mature B-cell ALL are virtually absent in DS, and recurrent chromosomal abnormalities are much less common. DS ALL has distinctive biologic features is supported by the recent discovery of activating somatic JAK2 mutations in approximately 20% of cases specific to this subgroup [1].

Conclusion

There is a varied spectrum of hematological malignancies in children with DS. A careful scrutiny of peripheral blood film and a close follow-up is warranted. Presence of blasts in the peripheral blood of a newborn with DS even if asymptomatic should raise the suspicion of TMD. Although TMD remits spontaneously, these cases require regular follow-up for detection of transformation to acute leukemia. In addition to TMD, AMKL, ALL and other types of AML are also common in DS.

References

1. Rabin KR, Whitlock JA (2009) Malignancy in children with trisomy 21. *Oncologist* 14:164–173
2. Massey GV, Zipursky A, Chang MN, Doyle JJ, Nasim S, Taub JW et al (2006) A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children Oncology Group (COG) study POG-9481. *Blood* 107: 4606–4613
3. Baumann I, Niemeyer CM, Brunning RD, Arber DA, Porwit A (2008) Myeloid proliferations related to Down syndrome. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al (eds) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. IARC, Lyon, pp 142–144
4. Roizen NJ, Patterson D (2003) Down's syndrome. *Lancet* 361: 1281–1289
5. Zipursky A, Brown EJ, Christensen H, Doyle J (1999) Transient myeloproliferative disorder (transient leukemia) and hematologic manifestations of Down syndrome. *Clin Lab Med* 19:157–167
6. Zipursky A, Brown E, Christensen H, Sutherland R, Doyle J (1997) Leukemia and/or myeloproliferative syndrome in neonates with Down syndrome. *Semin Perinatol* 21:97–101
7. Bhatt S, Schreck R, Graham JM et al (1995) Transient leukemia with trisomy 21. *Am J Med Genet* 58:310–314
8. Aier M, Zadeng T, Basu D, Biswal N, Nalini P (2002) Congenital leukemia in Down syndrome—a case report. *Indian J Pathol Microbiol* 45:355–357
9. Homans AC, Verissimo AM, Vlach V (1993) Transient abnormal myelopoiesis of infancy associated with trisomy 21. *Am J Pediatr Hematol Oncol* 15:392–397
10. Karandikar NJ, Aquino DB, McKenna RW, Kroft SH (2001) Transient myeloproliferative disorder and acute myeloid leukemia in Down syndrome. *Am J Clin Pathol* 116:204–210
11. Ahmed M, Sternberg A, Hall G, Thomas A, Smith O, O'Mar-caigh A et al (2004) Natural history of GATA 1 mutations in Down syndrome. *Blood* 103:2480–2489
12. Ge Y, Stout ML, Tatman DA, Jensen TL, Buck S, Thomas RL (2005) GATA1, cytidine deaminase, and the high cure rate of Down syndrome children with acute megakaryocytic leukemia. *J Natl Cancer Inst* 97:226–231