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Case report

Transient abnormal myelopoiesis without constitutional Down syndrome

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Abstract

Transient abnormal myelopoiesis (TAM) is a unique entity that usually occurs in children with Down syndrome (DS) or with trisomy 21 mosaicism. The somatic *GATA1* mutation is a distinct feature of TAM. At presentation, TAM can resemble congenital leukemia (CL), which unlike TAM has an extremely poor prognosis and requires prompt therapeutic interventions. Therefore, correct and timely distinction between the two entities is crucial. We report a case of a phenotypically normal infant diagnosed with CL during the first weeks of life that retrospectively was reassessed as TAM. No acute myeloid leukemia (AML) specific mutations were found except for trisomy 21 confined exclusively to leukemic blasts. Retrospectively *GATA1* mutation was also detected in malignant cells, but somatic genome appeared to be intact.

Keywords

Transient abnormal myelopoiesis, congenital leukemia, Down syndrome, myelodysplastic syndrome.

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Introduction

Transient abnormal myelopoiesis (TAM), otherwise transient myeloproliferative disorder/transient leukemia, is a unique entity that occurs in 4-10% of children with Down syndrome (DS) or trisomy 21 mosaicism [1, 2]. Somatic mutations in the *GATA1* gene are necessary for the development of TAM, which is a clonal pathology of megakaryoblasts infiltrating liver, spleen and peripheral blood [3, 4]. Although TAM usually resolves spontaneously within 3-6 months, up to 30% of patients develop myeloid leukemia within several years [4-6]. Usually, it is an acute megakaryoblastic leukemia (AMKL) evolving from the acquisition of one more somatic mutation besides *GATA1* and trisomy 21 [1, 5, 6]. Myelodysplastic syndrome (MDS) usually precedes AMKL.

The diagnosis of TAM is challenging: the symptoms usually mimic sepsis or congenital leukemia (CL). Diagnostic difficulties arise in distinguishing TAM from CL when there is no evidence of DS or genetic abnormalities of CL. A CL is an extremely rare pathology which occurs within the first 4-6 weeks of life and has a poor prognosis [7]. Thus accurate diagnosis is important to establish an appropriate treatment strategy.

Case report

A 12-hours-old male newborn (gestational age 36 weeks, birth weight 2,420 g) developed abnormal microcirculation, jaundice and respiratory distress. Physical examination revealed pallor, papular rash on the abdomen and legs, hepatosplenomegaly and a systolic heart murmur. No phenotypical features of DS were apparent. Complete blood count showed leukocytosis (71 × 10^9/L), anemia (hemoglobin 95 g/L), thrombocytosis (1,212 × 10^9/L) and blastema (68%). Examination of the cerebrospinal fluid revealed 33% of blasts. Bone marrow (BM) aspiration and flow cytometry counted 58% blasts expressing myeloid phenotype (CD45+bl, CD34+, CD38+, CD117+, CD4+bl, CD7+, CD33+, CD123+, CD13-, CD15-, CD64-, cMPO-, cCD3-). An aberrant CD4 and CD7 co-expression and atypical phenotype of HLA-DR were identified. However, no acute myeloid leukemia (AML) specific genetic aberrations (*BCR/ABL1*, *PML/RARA*, *AML1/ETO*, *FLT3 ITD*, *CBFB/MYH11*, *NPM1*) were detected. Single nucleotide polymorphism (SNP) array analysis of BM detected trisomy of chromosome 21 (**Fig. 1A**). The parents refused further genetic counseling, thus a congenital myeloid leukemia was diagnosed. As the boy's general condition was relatively stable, chemotherapy was omitted with the hope for a spontaneous remission. Supportive care was restricted to intravenous fluids and antibacterial therapy.

On the 8th day, pyodermia (yielding *Enterococcus faecalis* and *Staphylococcus epidermidis*) evolved. Leukocytosis (58-61 × 10^9/L) and blastema (15-18%) decreased, thrombocytopenia occurred, papular rash on the legs turned into vesicles (herpes simplex and varicella zoster PCR-DNA negative). A skin biopsy showed infiltrates in dermis of MPO/CD117 positive middle size cells with translucent cytoplasm and hemisphere shaped nucleus: CD117(+++) (cytoplasmic reaction); TdT(-); MPO(++) (cytoplasmic reaction) 30%; CD34(-); CD79a(-); CD10(-); Bcl2(+++) (cytoplasmic reaction); Pax5(-); Ki67 proliferative activity 30% (++) (nuclear reaction); CD3(-) (**Fig. 2A** and **Fig. 2B**). Treatment with local betamethasone and fusidic acid, intravenous vancomycin was administered. The clinical condition and blood counts were closely observed. At 2 months of age, the rash disappeared, leukocytosis decreased (8 × 10^9/L), although blastemia persisted (15%). The child was discharged for the out-patient follow-up.

During the first year of life, the boy remained in a stable condition, although regular transfusions were required. He became transfusion-free at 8 months of age. However, 3 months later, anemia, thrombocytopenia and neutropenia recurred (**Fig. 3**). Meanwhile, BM flow cytometry showed a persistent population of aberrant myeloid

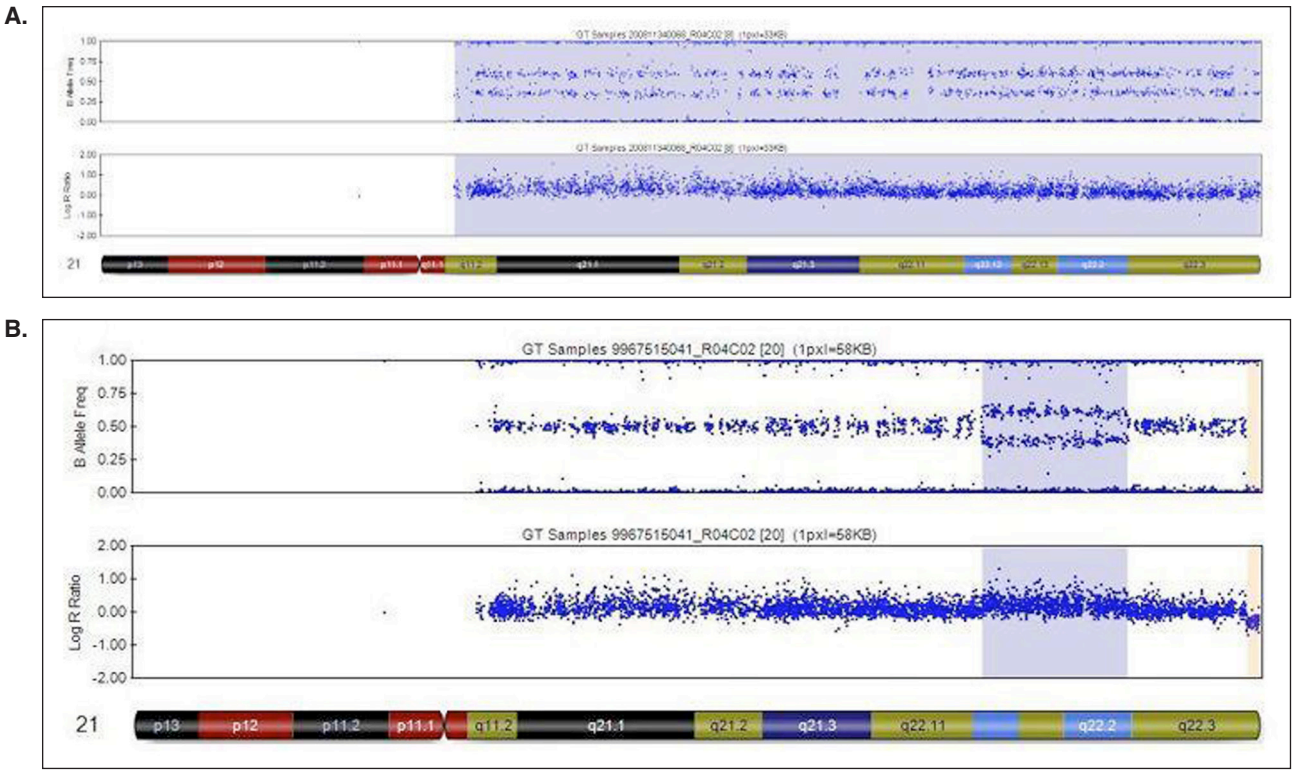

Figure 1. A. Trisomy of chromosome 21 (blue color) detected using Infinium HD whole-genome genotyping assay with the HumanCytoSNP-12 BeadChip. **B.** 6.2 Mb duplication (blue color) and 0.5 Mb deletion (red color) in the long arm of chromosome 21 detected using Infinium HD whole-genome genotyping assay with the HumanCytoSNP-12 BeadChip.

blasts (5%). At 14 months of age, trephine biopsy revealed a depressed granulopoiesis, erythropoiesis and hyperplasia/dysplasia of megakaryopoiesis (**Fig. 2C** and **Fig. 2D**). The findings were compatible with the diagnosis of MDS/AMKL. The SNP array of BM showed normal male karyotype.

At 16 months of age, the child's parents consented to the genetic counseling – chromosome analysis of skin fibroblasts showed a normal karyotype (46, XY). The repeated SNP array of BM revealed a defective 21 chromosome: 6.2 Mb duplication (which involves the *RUNX1* [*AML1*] gene) and 0.5 Mb deletion in the long arm of chromosome 21 (**Fig. 1B**). The same BM sample was evaluated at the Oxford Biomedical Research Centre, where a *GATA1* mutation was detected. Retrospectively DNA was extracted from the BM sample taken after birth and Sanger sequence analysis revealed a point mutation c.186C>G (p. Tyr62Ter). This was considered to be a deleterious change and was likely to be consistent with TAM/MDS, although the patient did not express dysmorphic features of DS.

A persistent myeloid clone, dysplasia of megakaryocytes, evolution of cytogenetic changes and transfusion-dependence were compatible with MDS. Repeated BM aspirate biopsies showed an increased expression of megakaryopoetic markers (CD41a was expressed in 20%, CD61 in 41% of blasts) that could be characteristic of AMKL. Assembling clinical, hematopoietic and laboratory findings, a diagnosis of MDS was documented.

Due to decreasing hematopoiesis and recurrent infections, a hematopoietic stem cell transplantation (HSCT) from a matched unrelated donor (10/10) was performed at the age of 21 months. The patient received myeloablative conditioning with intravenous busulphan, cyclophosphamide, melphalan (BuCyMel) and thymoglobulin. Soon after HSCT, the patient developed severe diarrhea and sepsis. Despite broad-spectrum antibacterial treatment, gut injury progressed to dynamic ileus and severe gastrointestinal bleeding. Neutrophil engraftment occurred on day +21, with donor chimerism of 99%. Nevertheless, the patient developed an acute graft-versus-host disease grade IV (diffuse skin erythema and gastrointestinal bleeding) resistant to methylprednisolone. Despite increased immune suppression and mesenchymal stem cell infusion,

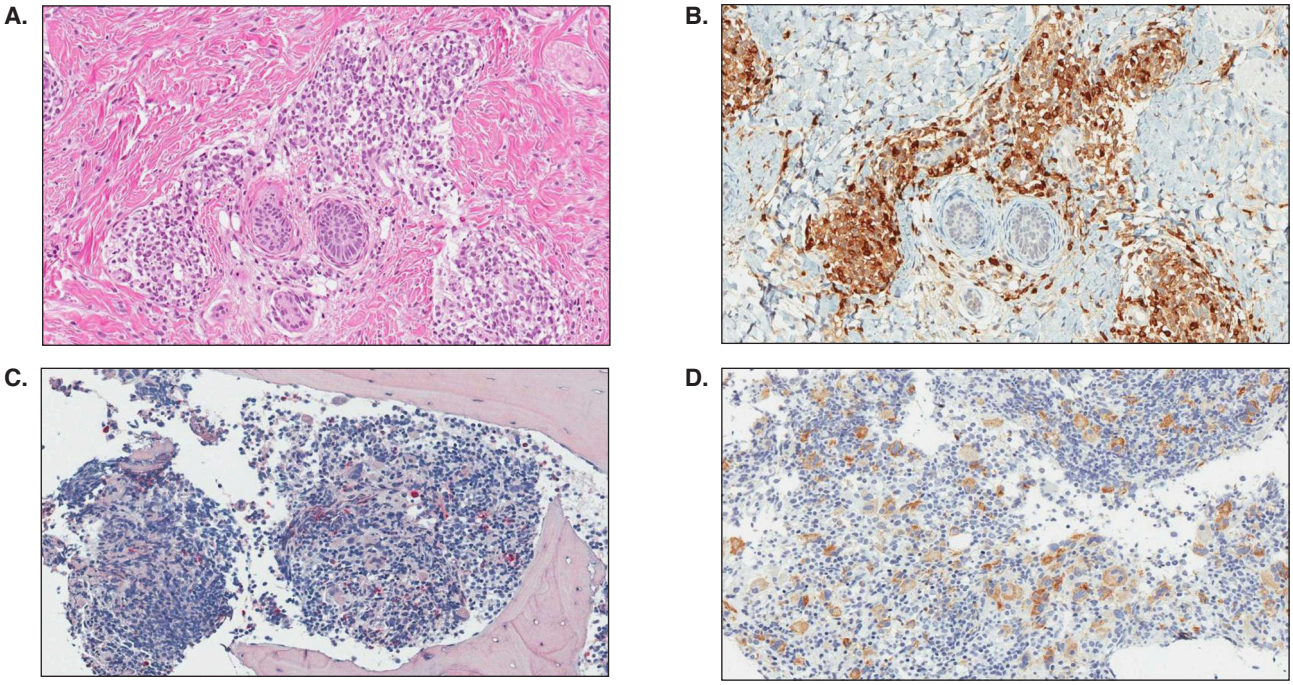

Figure 2. Findings of skin biopsy and trephine biopsy. **A.** Skin biopsy: hematoxylin eosin. 20x. The infiltrates of medium sized immature myeloid cells with ovoid or irregular nuclei and pale cytoplasm in the dermis. There are no erythroid precursors or megakariocytes. **B.** Skin biopsy: MPO immunohistochemistry. 20x. The infiltrates of immature myeloid cells are positive (as well as with CD117 and Bcl2). **C.** Trephanobiopsy: NASDE. 10x. Highly fragmented cellular bone marrow with only scattered granulocytes present. **D.** Trephanobiopsy: CD117 immunohistochemistry. 20x. Dysplastic megakariocytes show abberrant expression of CD117 (immature myeloid cell and mastocyte marker).

the boy developed multiple organ dysfunction syndrome and died on the day +32 following HSCT.

Discussion

TAM and CL are clinically similar entities that manifest soon after birth and cause a diagnostic dilemma. None of these conditions has pathognomonic symptoms and usually presents with pallor, poor sucking, cardio-respiratory distress, hepatosplenomegaly [8-10]. Leukemia cutis can be the first symptom of CL, particularly in AML cases [8]. Despite clinical similarities, TAM usually resolves spontaneously within three months of life while CL is resistant to treatment and often proceeds to a rapidly progressive downhill course, with a total 24 months survival rate of 23% [10], although there have been reported cases of spontaneous CL remission [11-13]. Thus, it imposes a therapeutic dilemma of whether to start chemotherapy or to "watch and wait".

The most helpful tool to discern between these pathologies is genetic testing. Up to 50% of newborns with AML have a rearrangement in the *MLL* gene on chromosome 11q23 [10]. TAM is much more common in neonates with DS or 21 chromosome mosaicism (4-10% of them are estimated to develop TAM) [1, 2]. TAM cases have mutations in the *GATA1* gene [3], which result in an abnormal proliferation of megakaryocytes and erythroid progenitors in the fetus [1, 14]. However, similar mutations of *GATA1* in cells without the trisomy 21 cause a different pathology, which manifests as anemia and neutropenia, but is not leukemogenic [1]. Thus abnormal fetal hematopoietic cells with a trisomic chromosome 21 need to acquire a mutation in *GATA1* to gain a proliferative advantage and to progress to TAM [1, 6]. Currently, several cases of TAM and subsequent AMKL in infants with an extra chromosome 21 and *GATA1* mutation in leukemic blasts without constitutional DS have been reported [4, 5, 15].

A diagnostic dilemma arises when the clinical manifestation of TAM mimics a classical acute leukemia (leukocytosis, blasts in BM and peripheral blood, organomegaly and skin lesions) with the absence of constitutional/mosaic trisomy 21 or *MLL* rearrangements. This was an issue in our case. Trisomy 21 was detected in the blast population; however, there were no other features of DS. Unfortunately, the parents refused genetic

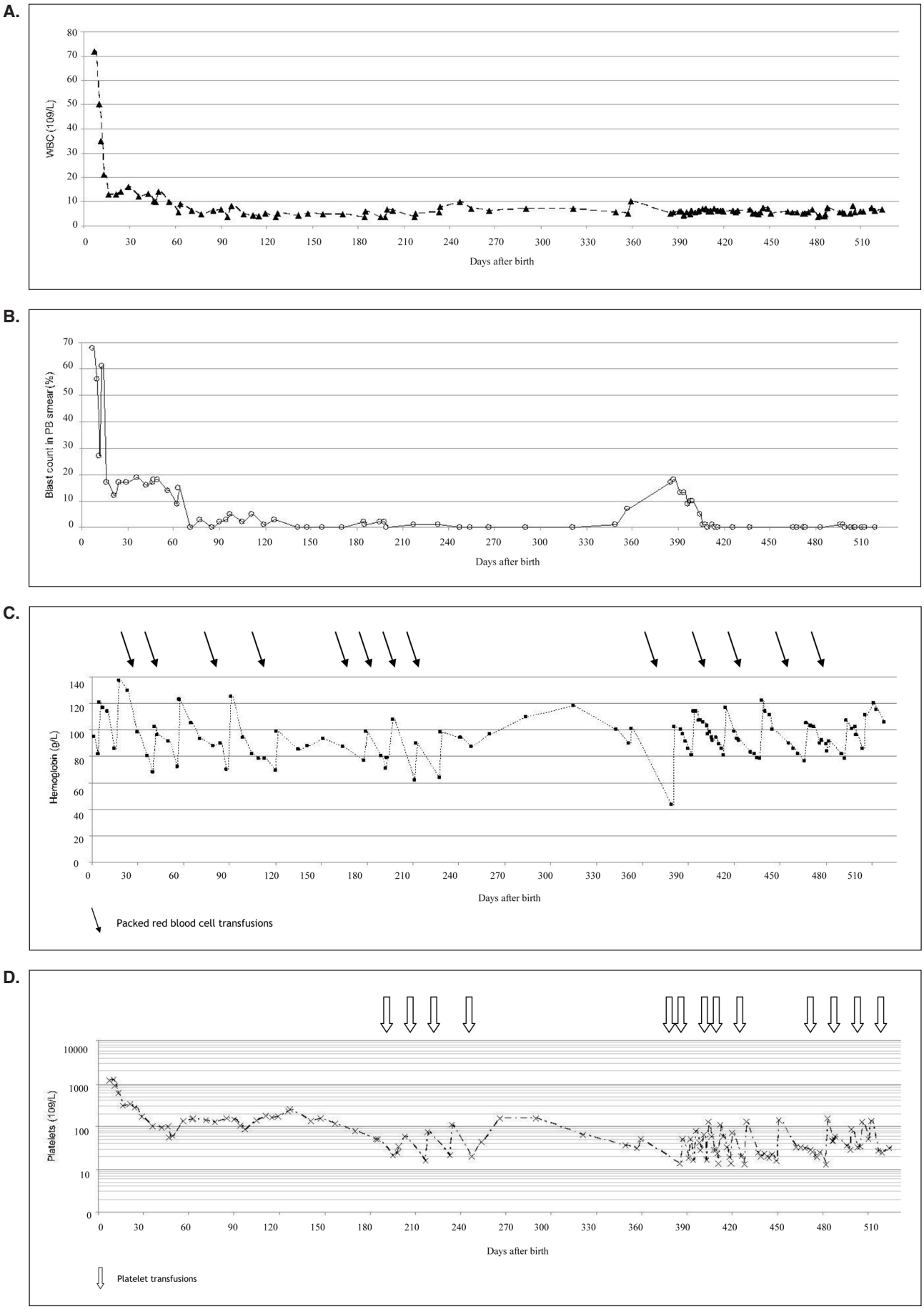

Figure 3. Dynamics of complete blood count during the course of the illness.

testing at the early stage of diagnosis that could have been helpful in determining whether 21 trisomy mosaicism or the *GATA1* mutation was present. Thus, without having sufficient arguments for TAM, a myeloid CL was diagnosed.

The optimal therapeutic approach is another challenging issue. As the baby was clinically stable and had no high-risk cytogenetic factors, the possibility of TAM was considered and the "watch and wait" strategy was chosen. Some reports on the initial management of CL favor a conservative approach assuming the possibility of spontaneous remission [12, 16]. The postponement of treatment allows the maturation of organs and systems; hence, infants become less vulnerable to chemotherapy [12, 13]. The improvement of the boy's condition at the age of two months supported the idea of a possible spontaneous remission of CL. Several hypotheses were proposed to elucidate this phenomenon (the tumor burden is low enough to be overcome by the patient's immune system [12, 13], the myeloid clone is not "sufficiently malignant", i.e., is capable to proliferate but not to renew itself [12, 13]). Once the abnormal leukocytes acquire additional genetic anomalies, a frank leukemia may ensue [12, 13]. Spontaneous remission of TAM occurs in 70% of cases and is explained by a preserved self-renewal capacity of double trisomy 21 and *GATA1* mutation [6]. A third additional mutation is needed to evolve TAM to AML (documented in 30% of cases of TAM within the first 4 years of life) [1, 3]. Sometimes abnormal hematopoiesis may persist presenting as an indolent MDS, which eventually turns into AML, usually during the first 12 months of life [1, 17]. The most common form of AML in children with DS is AMKL. The *GATA1* mutation is found in blasts of infants with DS and AML [3]. A similar scenario happened in our case. The child was clinically stable and transfusion independent approximately one year, however low blast count (up to 5%) was always present in BM. Afterward, his condition began to deteriorate and the trephine biopsy revealed features compatible with MDS.

MDS is a rare childhood disease, accounting for less than 5% of all hematopoietic neoplasms in children under 14 years old [3]. MDS associated with DS accounts for 25% of all childhood MDS and, according to WHO classification, MDS and AML in patients with DS are considered as a single unique entity, DS-related myeloid leukemia (DS-ML) [3].

As MDS in childhood is usually associated with genetic abnormalities [18, 19], genetic testing was also performed in our case. The karyotype of skin fibroblasts appeared to be normal (46, XY). However, the SNP array of BM revealed the defective 21 chromosome, and *GATA1* mutation was detected later on. The same mutation was found in the BM sample taken right after birth. These findings were considered to be compatible with TAM (previously diagnosed as CL), which evolved to MDS, though neither dysmorphic features of DS, nor mosaicism of trisomy 21 were found in this patient.

Children with MDS without DS have a poor prognosis because the disease is usually resistant to chemotherapy, fewer than 30% survive more than 3 years with chemotherapeutic treatment [3]. The only curative treatment for them is HSCT, which increases the 3-years disease-free survival up to 50% [18]. The treatment of choice is myeloablative therapy with BuCyMel, followed by matched family or matched unrelated donor HSCT [18]. In contrast, event-free survival in children with DS-ML is up to 80% [3]. This is related to overexpression of cystathionine β-synthase gene (localized in 21q22.3) on their blasts and low expression of cytidine deaminase with *GATA1* mutations, and thus higher sensitivity to chemotherapeutic agents, especially cytarabine [20]. Blasts are also sensitive to daunorubicin [3]. The standard chemotherapy that is administered in patients with AMKL causes a high incidence of treatment-related mortality in patients with DS [20].

The most delicate issue in our case was to choose the best treatment approach. The patient had a diagnosis of TAM, which evolved to MDS, but no supportive constitutional or mosaic of trisomy 21 was documented at any time. Thus, unusual adverse effects of chemotherapy were not expected. As MDS usually leads to AMKL and has a poor prognosis, the boy proceeded to an allogeneic HSCT. In the absence of DS, a myeloablative treatment with BuCyMel and thymoglobulin was chosen. Despite good initial engraftment, after a month the boy developed two episodes of sepsis that led to multiple organ dysfunction syndrome and lethal outcome. Though toxic complications following HSCT in MDS are common, the infant might have been more susceptible to myeloablative agents due to mutations in BM cells. Presumably, a reduced toxicity conditioning could spare the toxicity; however, the MDS-free outcome is still questionable.

Abbreviations

AMKL: acute megakaryoblastic leukemia
AML: acute myeloid leukemia
BM: bone marrow
BuCyMel: busulphan, cyclophosphamide, melphalan
CL: congenital leukemia
DS: Down syndrome
DS-ML: Down syndrome-related myeloid leukemia
HSCT: hematopoietic stem cell transplantation
MDS: myelodysplastic syndrome
SNP: single nucleotide polymorphism
TAM: transient abnormal myelopoiesis

Declaration of interest

The Authors have no conflicts of interest to declare and there is no financial interest to report.

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