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Case Report

A novel cryptic *CBFB-MYH11* gene fusion present at birth leading to acute myeloid leukemia and allowing molecular monitoring for minimal residual disease

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ABSTRACT

Acute myeloid leukemia (AML) with the inv(16)/t(16;16) karyotype is associated with a favourable prognosis, showing longer periods of complete remission and high overall survival rates. Here we report a four year old girl, who presented with pallor, a history of viral infections and pancytopenia, an abnormal karyotype, but initially no signs of leukemia. After one month, molecular diagnostics revealed a rare *CBFB/MYH11* fusion variant transcript type S/I, leading to the diagnosis of CBF AML. Additional FISH confirmed the presence of a cryptic *CBFB/MYH11* fusion. We developed a nested PCR test for the *CBFB/MYH11* fusion gene transcript S/I to monitor this patient for minimal residual disease. Eleven months after complete remission this transcript was still absent in peripheral blood samples.

Because at presentation this girl had no clinical signs of leukemia, but showed an abnormal karyotype with a cryptic *CBFB-MYH11*-fusion, we investigated whether this fusion was already present at birth. Therefore, the DNA fusion junction was cloned from diagnostic DNA and the patient-specific sequence was used to investigate the neonatal blood spot. Remarkably, the type S/I transcript of *CBFB/MYH11* was present in the neonatal blood spot, most likely being the first hit in leukemogenesis.

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1. Introduction

The pericentric inversion of chromosome 16 inv(16)(p13.1q22) or a balanced translocation t(16;16)(p13.1;q22) is seen in about 4% of patients with a de novo acute myeloid leukemia (AML), with the inversion being much more common (95%) than the translocation (5%). Both cytogenetic abnormalities result in a fusion gene between *CBFB* (core binding factor beta subunit) at 16q22 and *MYH11* (smooth muscle myosin heavy chain 11) on 16p13.1, leading to a chimeric CBFB/MYH11 protein. AML patients with an inv(16)/t(16;16) have been reported in all age groups, but most patients are relatively young; the median age is roughly 35 years [1].

The bone marrow of these AML patients usually shows monocytic and granulocytic differentiation and a variable number of eosinophils at all stages of maturation, without significant maturation arrest [1,2]. This AML subgroup was denoted by the French-American-British (FAB) classification as AML M4eo, the World Health Organization (WHO) 2016 has classified this subtype as “AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*” [3]. Patients harbouring an inv(16)/t(16;16) have a favourable prognosis, showing long periods of complete remission and high overall survival rates up to 70% [4].

At the molecular level, the fusion gene is formed by a 5′ sequence from *CBFB* at 16q22 with a 3′ sequence from *MYH11* at 16p13. There

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are more than 10 possible *CBFB-MYH11* fusion transcript variants identified, of which 85% of patients show the transcript type A [5,6]. The other, more rare, fusions show a more atypical cytomorphology, mostly with absence of the pathologic eosinophils, and therefore not recognized as FAB subtype M4eo. Due to the limited number of cases with a rare *CBFB-MYH11* fusion type, the biological and prognostic implications are still unclear [7].

In this study, we report on a girl who presented with pancytopenia, and showed to have an abnormal karyotype with a cytogenetic cryptic *CBFB-MYH11* fusion in her bone marrow, and therefore, diagnosed as AML. The fusion transcript appeared to be a rare variant type I, also known as type S/I [8]. We developed a patient specific marker for minimal residual disease (MRD) monitoring. Finally, by retrospective screening of the Guthrie card blood spot we showed that the *CBFB-MYH11* fusion transcript type S/I was already present at birth.

2. Case report

A four year old girl presented with pallor, a history of viral infections and pancytopenia, with a leukocyte count of 2.8×10^9/l and platelets 126×10^9/l and hemoglobin of 3.3 mmol/l. The peripheral blood smear revealed pancytopenia with some atypical lymphocytes. Paroxysmal nocturnal hemoglobinuria (PNH) and Fanconi's anemia were excluded. A bone marrow aspirate demonstrated mild dysplasia and megakaryocytosis, not indicative for a diagnosis of myelodysplasia nor acute leukemia (Fig. 1A). Immunophenotyping showed no increase of blasts. Based on these results a differential diagnosis was made including several infectious causes. However, serology could not confirm any of them (CMV, EBV, hepatitis, HIV, HSV, Parvo B19, toxoplasmosis and varicella zoster).

After a month her blood values had normalized (Hb 7.6 mmol/l, platelets 195×10^9/l, leukocytes 4.5×10^9/l). However, morphological examination of peripheral blood showed 12% Sudan Black positive blasts. Immunophenotyping of the peripheral blood showed the presence of 9% myeloblasts (CD13+, CD34+, CD117+, MPO+ and HLA-DR+, CD33−, and TdT weakly positive). The bone marrow aspirate showed 16% blasts and dysplasia, leading to the preliminary diagnosis of Refractory anemia with excess of blasts (RAEB) (Fig. 1B).

2.1. Cytogenetic studies

For karyotyping the patients' bone marrow aspirate were set up in two 24 h RPMI 1640 cultures, one unstimulated and one stimulated with G-CSF, IL3 and GM-CSF. After standard cytogenetic harvest and Giemsa-Trypsin-Giemsa banding 20 metaphase cells were analysed from both cultures. At presentation, the cytogenetic analysis showed in 6 of 20 cells an abnormal female karyotype with one aberrant chromosome 15 and two aberrant chromosomes 16 (Fig. 2A). Fluorescence in situ hybridisation (FISH) studies were performed according to the manufacturer's instructions in combination with our established laboratory protocol, using whole chromosome paints for chromosomes 15 and 16 (WC15 and WC16; Kreatech, Amsterdam, The Netherlands), and Telvysion probes 15q, 16p and 16q for the telomeres of chromosomes 15q, 16p and 16q, respectively (Molecular IL, Hoofddorp, The Netherlands). The aberrant chromosome 15 contained chromosome 16 material, including 16qter; one aberrant chromosome 16 had two 16pter signals, the other aberrant chromosome 16 contained 15q material. The karyotype was described according to ISCN 2016 [9] as: 46,XX,der(15)t(15;16)(?q22;?q24),?i(16)(p10),der(16)?i(16)(q10)t(15;16)(q?22;q?24)[6] /46,XX[14].

Since the meaning of this abnormal karyotype was unclear, we decided to repeat the investigations after one month. Cytogenetics revealed the same aberrant chromosomes 15 and 16 in 18 of 20 analysed cells. But now, also molecular studies were performed (see below) and showed a *CBFB-MYH11* fusion. Therefore, we performed additional FISH with LSI CBFB dual color break-apart rearrangement DNA probe (Abbott Molecular IL, Hoofddorp, The Netherlands) and CBFB MYH11 dual fusion translocation DNA probe (Cytocell Inc. Cambridge, UK). FISH demonstrated a CBFB-MYH11 fusion signal on the short arm of one aberrant chromosome 16, a CBFB signal on the derivative chromosome 15, suggesting a break within the CBFB-gene, and on the other chromosome 16, a CBFB signal on one chromosome arm and an amplified MYH11 signal on the other chromosome arm (Fig. 2B). The karyotype was described as: 46,XX,der(15)(15pter➔15q2?2::16q22➔16qter), der(16)(16pter➔16p13::16p13➔16q22::16p13➔16pter),der(16)(15qter➔15q2?2::16p13➔16qter).ish der(15)(3′CBFB+),der(16)(p13)(5′CBFB+,MYH11+) (q22)(MYH11++,3′CBFB-) ,der(16)(p13)(MYH11+)(q22)(CBFB+).

2.2. Molecular studies

Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed using the *CBFB* and *MYH11* primer pairs as described [10]. One month after initial presentation RT-PCR revealed an amplification product of approximately 300 bp between exon 4 of *CBFB* and exon 35 of *MYH11*, the rare fusion transcript type S/I [6,8,10]. Other molecular tests showed no *NPM1*, *FLT3*, *JAK2*, *EVI1* and *KIT* mutations. There was no DNA available from the sample at presentation.

To confirm the presence of the rare inversion 16 transcript type S/I 10 ng diagnostic bone marrow DNA was subjected to long-distance PCR using

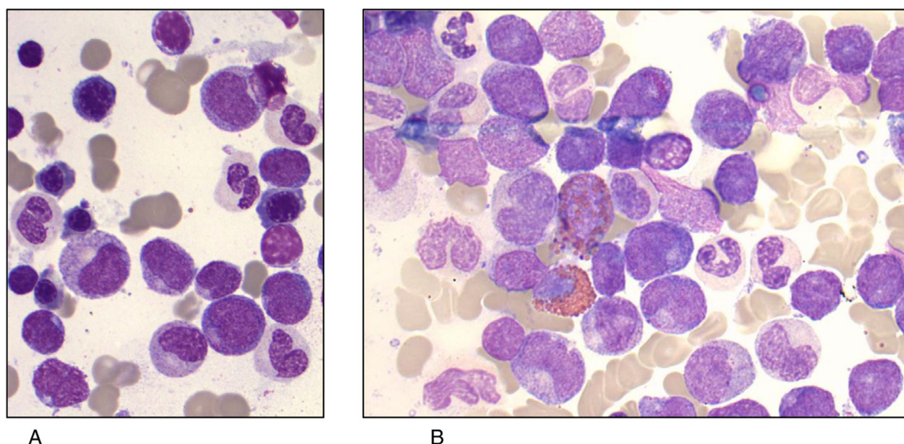

Fig. 1. Representative images of the bone marrow of the patient. A). Bone marrow aspirate at first presentation: no excess of blasts. B). Bone marrow aspirate after one month: more blasts and also abnormal eosinophils with large basophilic granules (in the middle), typical for inversion 16.

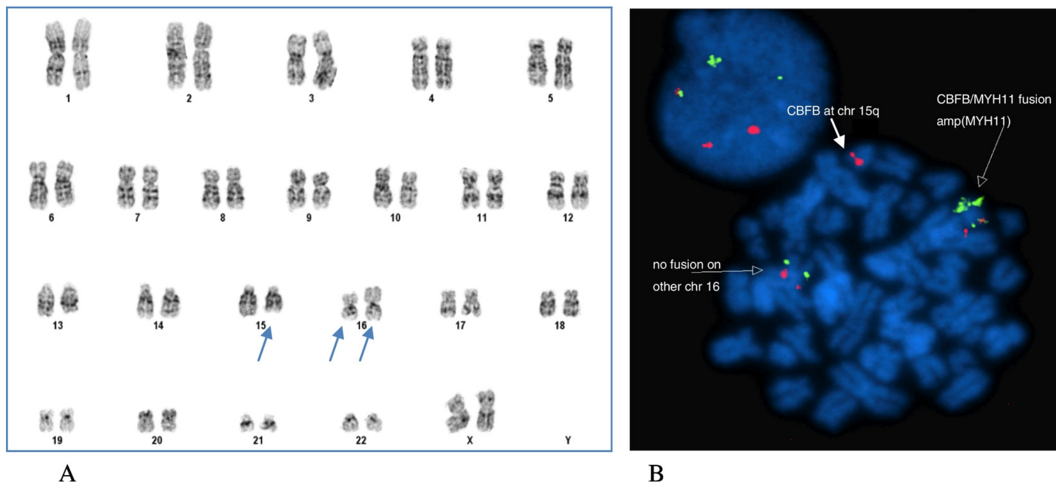

Fig. 2. Cytogenetic results. A). Representative karyotype, showing an aberrant chromosome 15 and two aberrant chromosomes 16 (arrows). B). FISH result with the CBFB/MYH11 Dual Color Dual Fusion Probe (Cytocell), showing a CBFB signal on the abnormal chromosome 15, and a CBFB/MYH11 fusion and MYH11 amplification on one abnormal chromosome 16.

High Fidelity AccuPrime Taq Polymerase (Life Technologies, Carlsbad, CA, USA) and the two diagnostic primers cmd1 and mmd2. The PCR product showed that exon 4 (nt 399) of *CBFB* was fused with intron 34 (nt 2134) of *MYH11* (CRCh38). Using a BigDye® Terminator Sequencing Kit and ABI-3730xl Genetic Analyser (Applied Biosystems®, Foster City, CA, USA), the resulting patient-specific 6 kb PCR product was sequenced in from the ends with the same and additional primers until the fusion junction was reached. Sequences were aligned by BLAST (www.ncbi.nlm.nih.gov/**blast**/). Sequence analysis of this ~6 kb fusion product confirmed that intron 4 of *CBFB* had broken and fused with intron 34 of *MYH11* (Fig. 3A and Supplementary Fig. 1A and B).

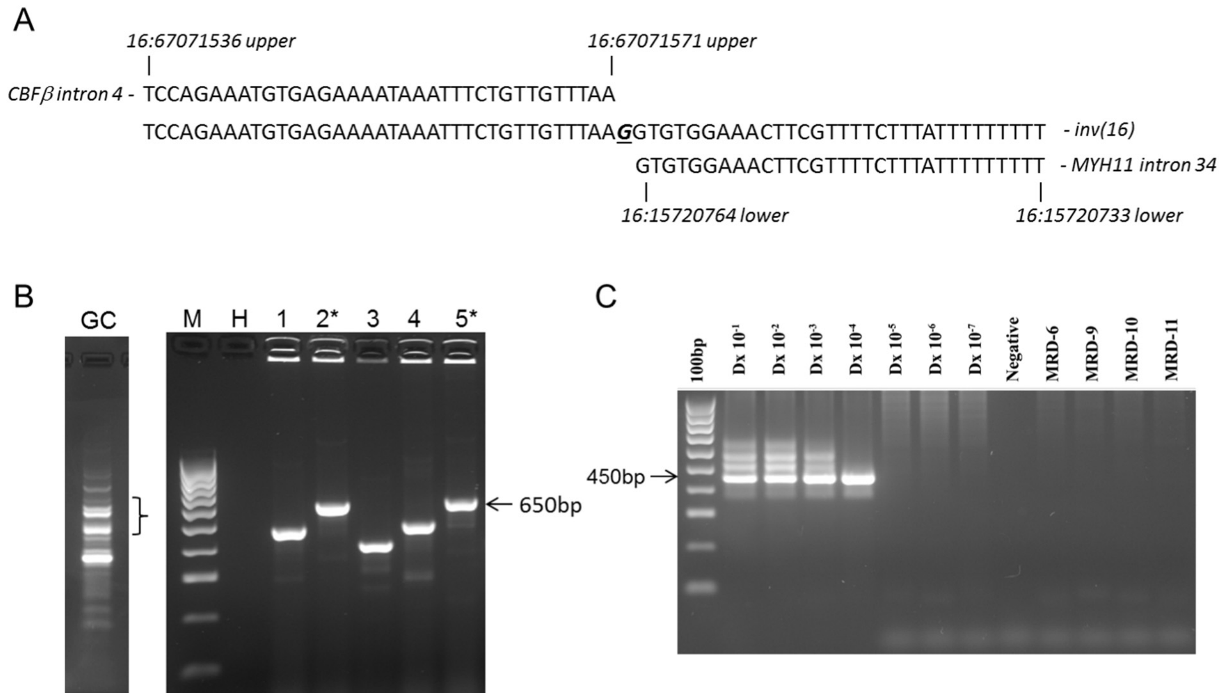

Fig. 3. In utero origins of inv(16). Method: About 3 mm diameter punches were cut from a dried blood spot and DNA was isolated using a QIAamp DNA micro kit essentially as described by the manufacturer (Qiagen, UK). Primer3plus (www.bioinformatics.nl/**primer3plus**/) was used to design suitable nested PCR primers situated on either side of the fusion: ExtFW – 5′-CCTGGCCCCACTACTTACCAGCTCT, ExtRV – 5′- TGATTCCGTTTTCTCATCTGCAACTGGGGA, IntFW – 5′- GGGCTCTGATCCAGTAGGGTTAGTGTCCTT, IntRV – 5′- GAACTCCTGG CCTCAAGTGATCCATTCTCC. Primer annealing was performed at 64 °C under standard PCR conditions. The final primer pair gave a fusion amplicon of approximately 450 bp, although it was not possible to isolate a sole specific PCR product due to the repetitive nature of this region throughout the genome. Purified PCR products around 450 bp were cloned into vector pCR2.1 using the TA cloning kit (Invitrogen, Carlsbad, CA), re-amplified and sequenced using forward and reverse M13 primers. The multiple cloning site of the vector accounts for the 201 bp size difference seen in the respective electrophoresis gels. DNA lane Markers used were HyperLadders I and IV (Bioline, London UK). A). DNA sequence of the patient-specific fusion of intron 4 of *CBFB* to intron 34 of *MYH11*. Co-ordinates are taken from the respective sequences in human GRCH38.p3. The underlined ***G*** nucleotide may derive from either *CBFB* or *MYH11* gene sequence. B). Backtracking of inv(16) to birth in a Guthrie Card. Left panel: PCR product of the patient's Guthrie Card DNA (GC) using primers that span the specific inv(16) breakpoint. Right panel: PCR products were cloned into vector pCR2.1, re-amplified and sequenced: 2 from 5 colonies harbour the specific inv(16) DNA fusion (marked by asterisks). M is HyperLadder IV. C). MRD analysis of samples at remission. Dilutions of the patient's diagnostic DNA and DNA prepared from remission samples taken at MRD months 6, 9, 10 and 11 were subject to the same inv(16) patient-specific PCR. Negative is the NTC and M is HyperLadder IV.

2.3. MRD monitoring

The fusion gene sequence was used as a patient-specific marker for minimal residual disease (MRD) monitoring. Again using PCR primers that spanned the fusion region we first performed PCR sensitivity assays on diluted diagnostic DNA and could detect the fusion gene down to a level of 1×10^{-4} (Fig. 3C). Serial dilutions of diagnostic DNA (10^{-1} to 10^{-7}) were subject to PCR using the internal primer set as described above and the same primer set was used to interrogate DNA prepared from patient blood samples taken at various stages during therapy, MRD-6, 9, 10 and 11 months. The fusion gene was not present in any of these four MRD samples (Fig. 3C). Eleven months after first complete remission following intensive treatment, the nested PCR *CBFB-MYH11* fusion transcript type S/I is still not detectable in her blood DNA.

2.4. Neonatal blood spot study

By retrospective screening of the neonatal blood spot, we obtained evidence that the *CBFB-MYH11* fusion was already present at birth. A nested PCR with specific primers designed across the breakpoint was performed on DNA isolated from the corresponding Guthrie card and showed the expected 450 bp product, along with a series of non-related fragments that result from the difficulty in finding adequate specificity of primers within this region (Fig. 3B, left). Cloning of these fragments into vector pCR2.1 allowed individual sequencing and identification of the exact fusion sequence in 2 from 5 colonies as that observed at diagnosis (Fig. 3B, right) and confirmation that the inversion had occurred in utero.

3. Discussion

According to WHO2016 the presence of a *CBFB-MYH11* gene fusion is classified as "AML with inv(16)/t(16;16) or t(16;16)(p13.1;q22);*CBFB-MYH11*". The bone marrow of these patients usually shows increased abnormal eosinophils, with large immature basophilic granules, mainly evident at the promyelocyte and myelocyte stages [2,3]. At initial presentation our patient showed only pancytopenia with some atypical lymphocytes and minor dysplasia of megakaryocytes, and was therefore not sufficient for diagnosis of leukemia. Although she had an abnormal karyotype in her bone marrow cells, this was not compatible with the diagnosis of leukemia, due to the absence of detectable aberrant myeloblasts.

One month later the bone marrow aspirate showed 16% blasts, morphologically with dysplasia. The girl was diagnosed with RAEB2. However, when molecular diagnosis showed a *CBFB-MYH11* variant transcript type S/I, the diagnosis was changed to "AML with inv(16)/t(16;16)" and the girl was treated according to the DB-AML-01 protocol.

Cytogenetic analyses revealed a complex karyotype with a cryptic *CBFB-MYH11* fusion. We hypothesize that this complex karyotype developed in two events (Fig. 4). First, a pericentric inversion in chromosome 16 between bands p13.1 (*MYH11*-gene) and q22 (*CBFB*-gene) occurred, followed by a three-way translocation, in which the 16q22-qter segment of the inversion-chromosome 16 was translocated to a chromosome 15 (at breakpoint 15q22), the 15q22-qter segment was translocated to the normal chromosome 16 (at breakpoint 16p13), and segment 16p13-pter from that chromosome 16 was relocated to the p-arm of the inversion chromosome 16. Next to this, FISH demonstrated an amplification of the *MYH11* region on the derivative chromosome 16 with the *CBFB-MYH11* fusion; the biological and prognostic significance of the *MYH11* amplification is not clear.

At presentation, apart from pallor and cytopenia, the girl had no signs of leukemia, although her karyotype was abnormal. However, a month later, the bone marrow contained 16% blasts, the same abnormal karyotype was present and molecular diagnostics revealed the *CBFB-MYH11* variant transcript S/I. It appeared that this fusion transcript was already present at initial presentation. We wondered whether

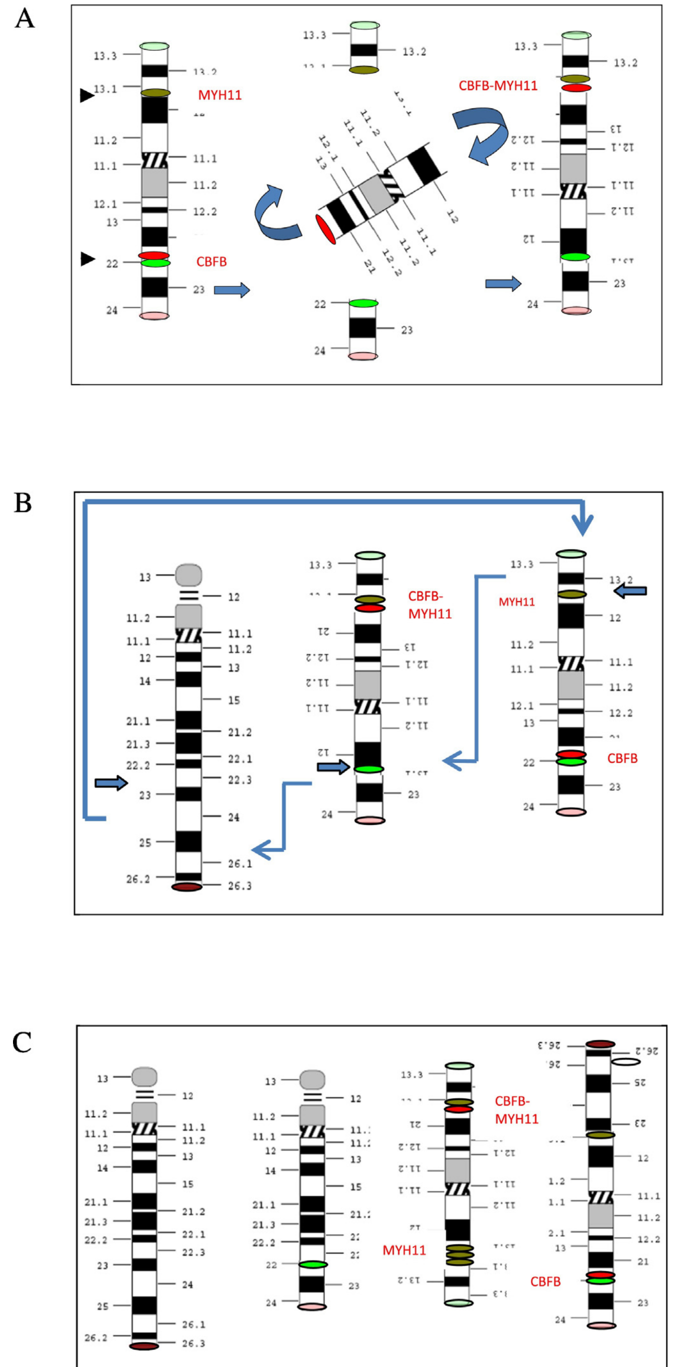

Fig. 4. Schematic representation of the cytogenetic events leading to the cryptic CBFB-MYH11 fusion. A). Event 1: inversion in one chromosome 16: inv(16)(p13q22) B). Event 2: a three-way translocation between a chromosome 15, the inv(16) and the normal chromosome 16. C). The final result: der(15)(15pter➔15q2?2::16q22➔16qter), der(16)(16pter➔16p13::16p13➔16q22::16p13➔16pter),der(16)(15qter➔15q2?2::16p13➔16qter) Legend of the used FISH probes: CBFB Break Apart probe. MYH11 probe. 16p subtelomeric probe. 16q subtelomeric probe. 15q subtelomeric probe.

this *CBFB-MYH11* fusion transcript was already present at birth, since Greaves and Wiemels [11] showed the presence of several leukemia fusion genes in archived neonatal blood spots of children with later onset of leukemia. Remarkably, the CBFB-MYH11 fusion variant transcript S/I was present in the Guthrie card blood spot, meaning that the fusion was already present at birth. To the best of our knowledge this is the first patient with a type S/I *CBFB-MYH11*-fusion transcript present at birth. It is known that the presence of fusion genes prenatally is insufficient to

cause disease, and additional induced genetic changes are required to overt leukemia [11]. This so-called 'two-hit' natural history of leukemia was described by Greaves [12]. It is assumed that biological stress from postnatal infections in combination with a dysregulated immune response may confer a growth advantage for a preleukemic clone, leading to its rapid expansion and an increased opportunity for the occurrence of a second mutation required for the development of childhood leukemia [13,14].

Until now, more than 10 possible *CBFB-MYH11* fusion transcripts variants have been reported, of which type A is present in about 85% of the patients with a inv(16)/t(16;16). As previously reported by Schnittger et al. [5] rare fusion transcripts of *CBFB-MYH11* often demonstrate an atypical bone marrow cytomorphology, which was also the case in our patient. The *CBFB-MYH11*-fusion variant type S/I present in our patient, was published first by Dissing et al. [8], and since then described in a few cases only [15]. It is believed that all patients with a *CBFB-MYH11* fusion have a favourable clinical course, regardless the fusion variant [4–7].

Fusion genes derived by chromosome translocation, such as TEL-AML1 and MLL-AF4 in ALL, or AML1-ETO and PML-RARa in AML, are common cytogenetic abnormalities in childhood leukemia and provide unique markers to follow up for minimal residual disease (MRD) [6]. Therefore, we developed a patient specific RT-PCR test to monitor our patient for MRD. Every three months a blood sample was tested. Eleven months after the end of treatment, the rare *CBFB-MYH11* variant type S/I was not detected in her blood and she is still in complete remission and now likely cured.

To summarize, in this report we describe a patient with a rare type S/I transcript of the *CBFB/MYH11* fusion as a result of a cytogenetic cryptic inv(16). Although she developed leukemia at the age of four years, *CBFB-MYH11* fusion transcript type S/I appeared to be already present at birth. A home-made patient specific PCR-test for this rare variant transcript allowed to monitor this patient for MRD. Eleven month after first complete remission the fusion gene transcript was still absent, and, after four years follow-up, also no blasts are present in peripheral blood.

Abbreviations

AML	acute myeloid leukemia
FISH	fluorescence in situ hybridization
PCR	polymerase chain reaction
MYH11	myosin heavy chain 11, smooth muscle
CBFB	core binding factor beta subunit
MRD	minimal residual disease

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ehpc.2017.09.001.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PJP drafted the paper and participated in the karyotyping and FISH studies; AHL performed the morphology and cytochemistry; TMW was involved in the immunophenotyping; JWW performed karyotyping and FISH experiments; PAM carried out the molecular diagnostic studies at diagnosis; MBM and AMF performed the inv16 DNA fusion cloning, neonatal blood spot and MRD experiments; SLB contributed in interpretation of the cytogenetic data; MAV, WAK and VdH were involved in diagnosis and treatment of the patient; MJW and GJLK have made contributions to conception and design of the paper; GJLK participated in the design and coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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