Guideline for management of non-Down syndrome neonates with a myeloproliferative disease on behalf of the I-BFM AML Study Group and EWOG-MDS


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Running heads
Guideline for management of IMD

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Author contributions
EJMB, BFG and MMHE designed the study and wrote the manuscript; EJMB performed literature review and included the data. BFG and MMHE supervised the study. AK, DJMH, CJP, MD, AC, EA and DNR included patients. AB and SCR reviewed the cytogenetic analyses. MMHE, CJP, DNR, BM, HH, SM, EJMB, CMN, JHK and DH participated in consensus meetings. All authors reviewed the manuscript and provided feedback.

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None.

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Transient myeloproliferative disease (TMD), Infantile myeloproliferative disease (IMD), transient leukemia (TL), non-Down, transient abnormal myelopoiesis (TAM), GATA1, Down syndrome, trisomy 21, JMML.
In neonates with myeloid hyperproliferation, apart from benign causes, Down syndrome (DS) related transient abnormal myelopoiesis (TAM), acute myeloid leukemia (AML) and juvenile myelomonocytic leukemia (JMML) are considered.\textsuperscript{1-3} Besides TAM, rarely, non-DS related transient myeloproliferative diseases occur, in which clinical decision making can be challenging.\textsuperscript{4} ‘TAM’, according to the WHO classification, only applies to children with (mosaic) Down syndrome.\textsuperscript{5} In the past, different terminology has been used in non-DS patients, such as transient myeloproliferative disease (TMD) and transient leukemia. Since distinction from TAM is important, and it is challenging to determine whether this disease will be transient, the consensus group decided to introduce the novel term “infantile myeloproliferative disease” (IMD), in order to be exclusive from TAM. Both TAM and IMD can usually be managed with a “watch and wait” strategy, while most full-blown AML or JMML cases require intensive treatment. We collected rare IMD cases from study groups collaborating in the International Berlin-Frankfurt-Münster AML Study Group (I-BFM AML SG). In addition, we reviewed the literature for neonatal cases of malignant myeloid hyperproliferation without DS. Based on these data, we developed, together with I-BFM AML SG and European Working Group of Myelodysplastic syndromes in Childhood (EWOG-MDS) members, by consensus, clinical recommendations for the diagnostic approach and current adequate classification of malignant myeloid hyperproliferation in infancy. This is meant to guide clinicians in choosing the right strategy, i.e. whether to “watch and wait” or start highly intensive treatment in individual cases.

We centrally collected detailed information from databases of collaborators of the I-BFM AML SG to identify clinical and genetic characteristics of additional, not yet reported, cases with IMD. Children younger than one year, diagnosed between 1990 and 2020, were included. Ethical approval and informed consent were obtained by each study group individually. Registration and data forms involved clinical features, hematological data, morphology and immunology, treatment, outcome and follow up data. Available written reports of cytogenetic findings were collected and centrally reviewed by Dr. A. Buijs (University Medical Center Utrecht) and Prof. Dr. S. Raimondi (St. Jude Children’s Hospital, Memphis). We identified 15 new cases of IMD with, in some cases, novel recurrent molecular aberrations (Table 1). No germline aberrations were identified; however, standardized diagnostics did not always include germline testing. Thirteen patients had somatic trisomy 21 (T21) with or without a GATA1 mutation, one patient had low mosaic somatic trisomy 8 and a SETD2 mutation and one patient was not tested for somatic aberrations. Notably, among the 15 newly added cases, in four patients, evaluation for GATA1 mutations was not performed.
The search for available literature and case reports of non-DS transient leukemia was performed in the Pubmed database. Publications indexed until January 1st, 2021 were included. Search terms included TMD, TAM and transient leukemia, used separately and combined with non-Down, non-Down syndrome, without Down syndrome. A cross-reference check was performed in key articles. We included 23 articles that described one or multiple patients that met our search criteria (Table 2). Unfortunately, also in these cases, routine testing of somatic GATA1 and potential germline mosaic T21 was not always performed.

Congenital/infant leukemia accounts for <1% of all childhood leukemias. When the rare event occurs that a neonate is suspected of myeloid leukemia, TAM or IMD, clinical decision making can be challenging. Here, representatives of the I-BFM AML SG together with JMML experts from the EWOG MDS, provide a clinically applicable consensus of diagnostic logistics for children younger than six weeks, based on literature and newly added cases from our international survey, which may support clinical decision making in individual cases (Figure 1). During two meetings with leading members from both the I-BFM AML SG and EWOG MDS relevant literature was discussed, and expert experience shared. We reached consensus on diagnostic strategies of neonates with myeloproliferation.

The differential diagnosis of myeloproliferation in infants includes, apart from (congenital) infections and other stressors, JMML, AML, TAM and other types of IMD. More frequent benign underlying conditions should be seriously considered before diagnosing a neonate with leukemia and starting intensive treatment (Figure 1). A medical history and physical examination are important to reveal first clues towards infectious causes, other factors inducing stress-hematopoiesis and genetic predisposition (presence of dysmorphic and congenital abnormalities). Physical examination will also reveal hepatosplenomegaly, fluid accumulation and/or skin infiltration. A total blood count and morphological assessment of the peripheral blood smear by an experienced hematologist or morphologist in an expert laboratory are mandatory, and at least peripheral blood immunophenotyping is advised.

If a malignant condition is conceivable, the most important challenge is to discriminate a rare transient case, where a “watch and wait” strategy may be justified, from an aggressive leukemia subtype that may require intensive treatment within a limited time span. First, a distinction between megakaryocytic and non-megakaryocytic leukemia is important, based on the morphology and immunophenotyping of the peripheral blood blasts. Megakaryocytic hyperproliferation (French-American-British - FAB - classification M7) can be recognized by moderately basophilic agranular
cytoplasm with blebs on morphology, combined with expression of CD41, CD42 and/or CD61 on flow cytometry. 

In case of megakaryocytic hyperproliferation, germline T21 and GATA1 mutations may point towards TAM. TAM blasts can also present without megakaryocytic markers, FAB M0 (undifferentiated). In TAM, early onset and hepatosplenomegaly with monoclonal megakaryocytic hyperproliferation with T21 and a GATA1 mutation can be confirmed. The origin of TAM lies in the fetal liver, which is why, in most cases, peripheral blood sampling is sufficient for a diagnosis and a bone marrow puncture is unnecessary. Without life-threatening disease, a “watch and wait” policy with close monitoring, including regular physical examination and blood counts, is justified. Low-dose cytarabine treatment is advised in case of multiorgan failure, high WBC >100 x 10⁹/l, hepatopathy (high bilirubin/transaminases, ascites), severe hepatosplenomegaly, hydrops fetalis, pleural or pericardial effusions, renal failure, or disseminated intravascular coagulation. This treatment does not prevent development of ML-DS (myeloid leukemia related to Down syndrome), but substantially reduces mortality in symptomatic patients. After remission, follow-up is advised every three months until the age of four years, because of a 20% chance of ML-DS development during that life span. ML-DS requires more intensive treatment, however with high success rates.

In megakaryoblastic cases without germline (mosaic) T21 and a GATA1 mutation, a bone marrow puncture can be considered. Furthermore, additional mutational analyses for recurrent germline or somatic IMD-related aberrations (such as somatic T21), as well as analyses for recurrent infant AML translocations, are advised (Figure 1; discussed below).

In neonatal non-M7/M0 hyperproliferation, first, discrimination between JMML and AML, and in rare cases, a non-M7 IMD, is important. Bone marrow investigation can be considered for immunophenotyping, karyotyping, fluorescence in situ hybridization (FISH) and targeted mutational analyses. Collection of germline material for sequencing discrimination purposes is advisable.

In monocytic proliferation, JMML diagnostics are advised, and morphology of the peripheral blood smear, which shows (meta)myelocytes and nucleated red cells combined with the clinical phenotype, is of utmost importance. Dysmorphic features of RAS pathway related syndromes are important to be identified. Other JMML characteristics are splenomegaly, an elevated fetal hemoglobin value and a normal or moderately increased bone marrow blast count. JMML is in 90% of the cases characterized by mutations in PTPN11, NRAS, KRAS, NF1 or CBL. Germline CBL, KRAS, NRAS, PTPN11
or RIT1 mutations indicate a RAS pathway driven JMML, in which spontaneous remission often occurs and a “watch and wait” policy may be considered if clinically feasible.\textsuperscript{3} In contrast, patients with a somatic RAS driver mutation commonly have aggressive disease requiring allogeneic hematopoietic stem cell transplantation in most cases.\textsuperscript{3}

When the clinical picture of a non-megakaryoblastic leukemia is not consistent with JMML, IMD and AML may be seriously considered. Such cases mainly consist of monoblastic AML (FAB M5; immunophenotype CD4+CD11b+CD64+), characteristically present with leukemia cutis, hepatosplenomegaly, hyperleukocytosis and KMT2A-fusions, and require AML-directed chemotherapy.\textsuperscript{2, 5, 6, 10} A diagnostic bone marrow puncture is advised for molecular blast cell characterization. Recurrent translocations, characteristic for infant AML, are t(1;22)(p13.3;q13.1)/RBM15-MKL1, 11q23.3/KMT2A-translocation and t(8;16) (p11.2; p13.3)/KMT2A-CREBBP. Furthermore, t(8;21)(q22;q22)/RUNX1-RUNX1T1, t(8;1)(p11;q22), t(5;6)(q31;q21), t(6;17)(q23;q11.2) and t(X;6)(p11.1;q23) have been identified.\textsuperscript{2, 10-12} Most of these karyotypes are associated with aggressive AML, requiring intensive treatment.\textsuperscript{13-15}

Interestingly, in rare myeloid leukemia cases a “watch and wait” policy can be considered, as illustrated by reports of incidental cases with successful “watch and wait” strategies (Table 1,2). These cases include monoclonal infant AML M4/M5-cases with somatic t(8;16); however, t(8;16) can also be present in full-blown AML.\textsuperscript{10} IMD associated with germline THPO mutations should be seriously considered in families with a positive history of essential thrombocytosis and myeloproliferative disease in elderly (Table 2). Furthermore, we found increasing evidence on somatic T21, GATA1 mutations and del(8)(q23.2q24) in IMD (Table 1,2). SNP array analysis can aid in the identification of subclonal T21 with small clone sizes. Finally, some aberrations have only been described once; nevertheless, they might become recurrent, such as a del(5q), SETD2 or germline NSD1 mutation (Table 1,2).

In conclusion, this review and consensus based diagnostic guideline may aid in clinical decision making for the rare infant cases with myeloid hyperproliferation (Figure 1), especially if a “watch and wait” policy is considered and clinically feasible. Despite our extensive research, we were only able to include a limited number of patients, which emphasizes the rarity of the disease and makes general conclusions challenging. To identify these individual cases, extensive and ongoing (international) collaboration of pediatric oncologists, cytogeneticists, immunologists, molecular biologists and clinical geneticists is mandatory for clinical decision-making, development of diagnostics tools and treatment. Genomic sequencing can identify novel aberrations that could be recurrent. We here
present a consensus for the preferred diagnostic logistics, based on a broad international consortium with clinicians and investigators from the I-BFM AML SG and EWOG MDS. This consensus may support decision-making in these rare infants presenting with myeloproliferative disease.

Appendix

European Working Group of MDS in childhood (EWOG-MDS) members are: F. Locatelli, B. de Moerloose, M. Dworzak, C.M. Niemeyer, H. Hasle and M.M. van den Heuvel-Eibrink

References


<table>
<thead>
<tr>
<th>UPN</th>
<th>Studygroup</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>FAB</th>
<th>Genetic tests</th>
<th>Germline</th>
<th>Somatic</th>
<th>Treatment</th>
<th>CR/Event</th>
<th>Vital status (FU/time)</th>
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<tbody>
<tr>
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<td>Slovakia</td>
<td>Newborn</td>
<td>F</td>
<td>HSM</td>
<td>M7</td>
<td>FISH, PCR</td>
<td>Normal</td>
<td>T21</td>
<td>N/A</td>
<td>CR</td>
<td>Alive (6.5 years)</td>
</tr>
<tr>
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<td>1,5 months</td>
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<td>HSM</td>
<td>M7</td>
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<td>Normal</td>
<td>T21</td>
<td>None</td>
<td>CR</td>
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</tr>
<tr>
<td>3</td>
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<td>F</td>
<td>HGM, CL, VSD (Agalda syndrome)</td>
<td>N/A</td>
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<td>T21</td>
<td>Low-dose AraC</td>
<td>Died (at 18 months)</td>
<td></td>
</tr>
<tr>
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<td>None</td>
<td>M7</td>
<td>Karyotype FISH</td>
<td>Normal</td>
<td>T21, GATAI</td>
<td>None</td>
<td>CR</td>
<td>Alive (9 years)</td>
</tr>
<tr>
<td>5</td>
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<td>N/A</td>
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<td>T21, GATAI</td>
<td>None</td>
<td>CR</td>
<td>Alive (3 years)</td>
</tr>
<tr>
<td>6</td>
<td>Austria</td>
<td>5 days</td>
<td>F</td>
<td>None</td>
<td>M7</td>
<td>Karyotype, FISH, PCR</td>
<td>Normal</td>
<td>T21, GATAI</td>
<td>None</td>
<td>CR</td>
<td>Alive (9 years)</td>
</tr>
<tr>
<td>7</td>
<td>Slovakia</td>
<td>Newborn</td>
<td>F</td>
<td>HM, CL</td>
<td>M1</td>
<td>FISH, PCR</td>
<td>Normal</td>
<td>T21, GATAI</td>
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<td>CR</td>
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</tr>
<tr>
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<td>CL</td>
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<td>None</td>
<td>CR</td>
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<tr>
<td>9</td>
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<td>N/A</td>
<td>M</td>
<td>HGM, CL</td>
<td>N/A</td>
<td>Not tested at time of IMD</td>
<td>Normal</td>
<td>N/A</td>
<td>None</td>
<td>AML (at 3 years) with somatic T21 and GATAI-mutation: AML 8F 2004 protocol CR at day 15; SCT.</td>
<td>Alive (6.5 years)</td>
</tr>
<tr>
<td>10</td>
<td>Spain</td>
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<td>M</td>
<td>Few petechiae</td>
<td>M7</td>
<td>Karyotype, FISH, CGH, NGS (117 genes)</td>
<td>Normal</td>
<td>SETD2, trisomy 8</td>
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<td>CR, developed AML (at 4 months), CR after first induction</td>
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<td>6 weeks</td>
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<td>N/A</td>
<td>Karyotype, PCR</td>
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<td>None</td>
<td>CR</td>
<td>Alive (3 years)</td>
</tr>
<tr>
<td>12</td>
<td>Germany</td>
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<td>None</td>
<td>N/A</td>
<td>Karyotype, PCR</td>
<td>Normal</td>
<td>T21 (mosaic BM), GATAI</td>
<td>None</td>
<td>CR</td>
<td>Alive (1 year)</td>
</tr>
<tr>
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<td>ASD II</td>
<td>N/A</td>
<td>Karyotype, FISH, PCR</td>
<td>Normal (fibroblasts)</td>
<td>Mosaic T21, GATAI</td>
<td>Prediction</td>
<td>CR (8 weeks), developed AML (at 10 months)</td>
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<td>14</td>
<td>Germany</td>
<td>3 weeks</td>
<td>F</td>
<td>None</td>
<td>N/A</td>
<td>Karyotype, FISH, PCR</td>
<td>Normal</td>
<td>T21, GATAI</td>
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<td>CR</td>
<td>Died (2 days after AML diagnosis)</td>
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<tr>
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<td>Germany</td>
<td>Newborn</td>
<td>F</td>
<td>None</td>
<td>N/A</td>
<td>Karyotype, FISH, PCR</td>
<td>AML (46,XX, i(1;11)(p11.1); [15]</td>
<td>T21, GATAI</td>
<td>None</td>
<td>CR</td>
<td>Alive (1 year)</td>
</tr>
</tbody>
</table>

*Inclusion criteria: histological non-TAM, non-JMM cases, cured with no/only symptomatic treatment, age <1 year at diagnosis, diagnosed from 1990-2020. Exclusion criteria: transient abnormal myelopoiesis (TAM) according to WHO definition. 1. Questioned for hepatosplenomegaly (HSM), intravascular coagulation, cutaneous lesions (CL), central nervous system (CNS)-involvement or other extramedullary disease. 2. GATAI not tested in every case. 3. IMD diagnosis not definite, was made in retrospect, based on blood counts. 4. In initial diagnosis acute lymphoblastic leukemia (ALL). AML: acute myeloid leukemia; araC: cytarabine; SCT: stem cell transplantation; ASD: atrial septum defect; BM: bone marrow; CGH: comparative genomic hybridization; CR: complete remission; DS: Down syndrome; F: female; PM: French-American-British classification; FISH: fluorescence in situ hybridization; FU: follow-up; HM: hepatomegaly; M7: infantile myeloid prolifeative disease (unrelated to Down syndrome); M: male; N/A: data not available; NGS: next generation sequencing; PCR: polymerase chain reaction; T21: trisomy 21; UPN: unique patient number; VSD: ventricular septum defect; WHO: World Health Organization.
Table 2. Previously reported IMD-cases without germline (mosaic) trisomy 21 from literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>FAB/F</th>
<th>Genetic tests</th>
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<th>Treatment</th>
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<td>Basu</td>
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<td>None</td>
<td>N/A</td>
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<td>GA Tα1</td>
<td>No ne</td>
<td>CR</td>
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<tr>
<td>Houwing</td>
<td>17</td>
<td>F</td>
<td>immature monoblasts</td>
<td>N/A</td>
<td>t(Ph,mos), GATA1 screening</td>
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<td>Alive (3 years)</td>
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<tr>
<td>Van Dijken</td>
<td>18</td>
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<td>None</td>
<td>Familial monosomyosis (8p)</td>
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<td>No ne</td>
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</tr>
<tr>
<td>Silva</td>
<td>19</td>
<td>M</td>
<td>M/HSM</td>
<td>N/A</td>
<td>Not specific</td>
<td>NS (clinical diagnosis)</td>
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<td>No ne</td>
<td>CR</td>
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<td>Bertrums</td>
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<td>M</td>
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<td>N/A</td>
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<td>Del(8)(q23.2q24) &amp; T21</td>
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<td>No ne</td>
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<td>T21</td>
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<td>No ne</td>
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<tr>
<td>Philpott</td>
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<td>No ne</td>
<td>CR</td>
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<td>Alive</td>
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<td>T21</td>
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<td>No ne</td>
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<tr>
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<td>No ne</td>
<td>No ne</td>
<td>CR</td>
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<td>Garnthen</td>
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<td>T21</td>
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<td>No ne</td>
<td>CR</td>
<td>Alive (2 months)</td>
</tr>
<tr>
<td>Sakurai</td>
<td>28</td>
<td>M</td>
<td>Myeloblastic</td>
<td>N/A</td>
<td>T21</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (7 months)</td>
</tr>
<tr>
<td>Yawata</td>
<td>29-30</td>
<td>M</td>
<td>Myeloid</td>
<td>N/A</td>
<td>T21</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (2 months)</td>
</tr>
<tr>
<td>Rosene</td>
<td>31-32</td>
<td>M</td>
<td>None</td>
<td>N/A</td>
<td>Myeloblastic</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (1.5 years)</td>
</tr>
<tr>
<td>Dossela</td>
<td>33-34</td>
<td>F</td>
<td>M/HSM</td>
<td>N/A</td>
<td>Myeloblastic</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (3 months)</td>
</tr>
<tr>
<td>Roseman</td>
<td>35-36</td>
<td>M</td>
<td>None</td>
<td>N/A</td>
<td>Myeloblastic</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (4 months)</td>
</tr>
<tr>
<td>Apollone</td>
<td>37-38</td>
<td>F</td>
<td>M/HSM</td>
<td>N/A</td>
<td>Myeloblastic</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (5 months)</td>
</tr>
<tr>
<td>Apollone</td>
<td>39</td>
<td>M</td>
<td>Myeloblastic</td>
<td>N/A</td>
<td>Myeloblastic</td>
<td>Del(8)(q23.2q24) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (5 months)</td>
</tr>
<tr>
<td>Cheneau</td>
<td>40</td>
<td>M</td>
<td>CL</td>
<td>N/A</td>
<td>Myeloblastic</td>
<td>Del(8)(q23.2q42) &amp; T21</td>
<td>No ne</td>
<td>No ne</td>
<td>CR</td>
<td>Alive (5 months)</td>
</tr>
<tr>
<td></td>
<td>First Name</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Molecular Testing</td>
<td>Cryplic Translocation</td>
<td>Died (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
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<td>------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Barrett</td>
<td>Newborn</td>
<td>F</td>
<td>(myeloid sarcoma)</td>
<td>M4</td>
<td>Karyotype, FISH (also in CR), molecular testing</td>
<td>No</td>
<td>Alive (23 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Nakashima</td>
<td>Newborn</td>
<td>M</td>
<td>None</td>
<td>Megakaryocytic</td>
<td>FISH, chromosomal microarray, GATA1-analysis on UCB</td>
<td>No</td>
<td>CR</td>
<td>Alive (2 years)</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Schifferli</td>
<td>Newborn</td>
<td>M</td>
<td>Blasts in cerebral spinal fluid</td>
<td>M7</td>
<td>FISH, BAC-array, SNP-array</td>
<td>13q12.11 deletion (300 kbp; 3 genes: GJB6, MIR4499, OR1L1)</td>
<td>No</td>
<td>CR</td>
<td>Alive (3 years)</td>
</tr>
<tr>
<td>55</td>
<td>Lukes</td>
<td>Newborn</td>
<td>M</td>
<td>HS, CL</td>
<td>Megakaryocytic</td>
<td>FISH, WES, whole transcriptome sequencing</td>
<td>Normal</td>
<td>GATA1, MLK1, SPIRE2 &amp; FN1 mutations</td>
<td>No</td>
<td>CR</td>
</tr>
</tbody>
</table>

* Check for hepatosplenomegaly (HSM), intravascular coagulation, cutaneous lesions (CL), CNS-involvement or other extra-medullary disease. ^1 Uncertain whether this was germ line mosaic. ^2 Karyotype not tested. ^3 Satellite Y chromosome. ^4 The case was previously described, at that time Sotos diagnosis was not known yet (WES was performed after). AML: acute myeloid leukaemia; CCR: cytoreduction; Bac: bacterial artificial chromosome; CR: complete remission; CT: chemotherapy; F: female; FA8: French-American-British classification; FISH: fluorescence in situ hybridisation; FU: follow-up; HM: hepatomegaly; IP: immunophenotype markers; IMD: infantile myeloproliferative disease (unrelated to Down syndrome); M: male; MDS: myelodysplastic syndrome; M1-DS: myeloid leukaemia related to Down syndrome; N/A: data not available; NGS: next generation sequencing; NS: Noonan syndrome; PS: peripheral blood; PCR: polymerase chain reaction; RT-PCR: reverse transcription PCR; SCT: stem cell transplantation; SNP: single nucleotide polymorphism; T21: trisomy 21; UCB: umbilical cord blood; UPN: unique patient number; WES: whole exome sequencing.

References:
- Orio R et al., Eur. J. Pediatr., 2015;
- Salvatore G et al. Oncol. Lett. 2017;
- Yuzawa K et al., Pediatr. Blood Cancer. 2020;
- Tsai MH et al. Indian J Pediatr. 2015;
- Coenen EA et al. Blood 2013;
Figure 1. Consensus on diagnostics in neonates with myeloblasts based on available literature and newly added cases

1 In case of doubt always refer to a clinical geneticist. 2 If these are not identified, deep sequencing techniques [SNP-array, RNA-seq, WGS] should be considered. Sporadic identified aberrations are listed in text. 3 Can be both transient and aggressive leukemia. 4 Only if clinical presentation allows, with close monitoring of clinical symptoms and regular blood counts. 5 In case of doubt consider consulting international study group [International Berlin-Frankfurt-Münster AML Study Group, European Working Groups of Myelodysplastic syndromes]. References on individual IMD-related aberrations can be found in Table 2.6-14,16

AML: acute myeloid leukemia; BM: bone marrow; CT: chemotherapy; FISH: fluorescence in situ hybridization; HSCT: hematopoietic stem cell transplantation; IMD: infantile myeloproliferative disease unrelated to Down syndrome; JMML: juvenile myelomonocytic leukemia; NS: Noonan syndrome; PB: peripheral blood; SNP: single nucleotide polymorphism; T21: trisomy 21; TAM: transient abnormal myelopoiesis related to Down syndrome; WGS: whole genome sequencing
Neonate (<6 weeks) with myeloproliferation in peripheral blood

- Medical history: hypoxia, infections
- Physical examination:
  - Dysmorphic features
  - Hepatosplenomegaly, skin infiltration
- PB:
  - Total blood count
  - Morphology
  - Immunophenotyping

Suspicion of leukemia

- M7/M0
- Non-M7/M0

Non-M7/M0

- Consider BM: blasts (+ germline material)
  - Karyotyping, FISH
  - Mutational analysis

Recurrent germline/somatic IMD-related aberrations:
- Germline THPO mutation, somatic +21, t(8;16)(p11.2;p13.3), GATA1 mutation and possibly del(8)(q23.2;q24).

Germline (mosaic) T21 & GATA1

DS-TAM

- Consider symptomatic treatment
  - Watch & Wait

IMD

- DS-TAM
  - Watch & Wait

JMML

RASopathies:
- germline CBL, KRAS, NRAS, PTPN11 or RIT1 mutation

AML

- Consider symptomatic treatment
  - Watch & Wait
  - CT

Alternative diagnoses

Consider:
- Infection
- Hemolysis
- Asphyxia
- Other congenital neoplasms

Watch & Wait
- Consider HSCT