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# Leukaemia Section

## Review

# Myeloid proliferations in Down syndrome

**Karen M. Chisholm**

Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA; karen.chisholm@seattlechildrens.org

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## Abstract

Review on myeloid proliferations related to Down syndrome, with data on clinics, pathology, and involved genes.

**KEYWORDS**
Down syndrome, leukemia, megakaryoblastic leukemia, myeloid leukemia, transient abnormal myelopoiesis.

## Identity

**Other names**
Myeloid proliferations related to Down syndrome: transient abnormal myelopoiesis and myeloid leukemia associated with Down syndrome
Transient abnormal myelopoiesis was previously known as "transient myeloproliferative disorder" and "transient leukemia".

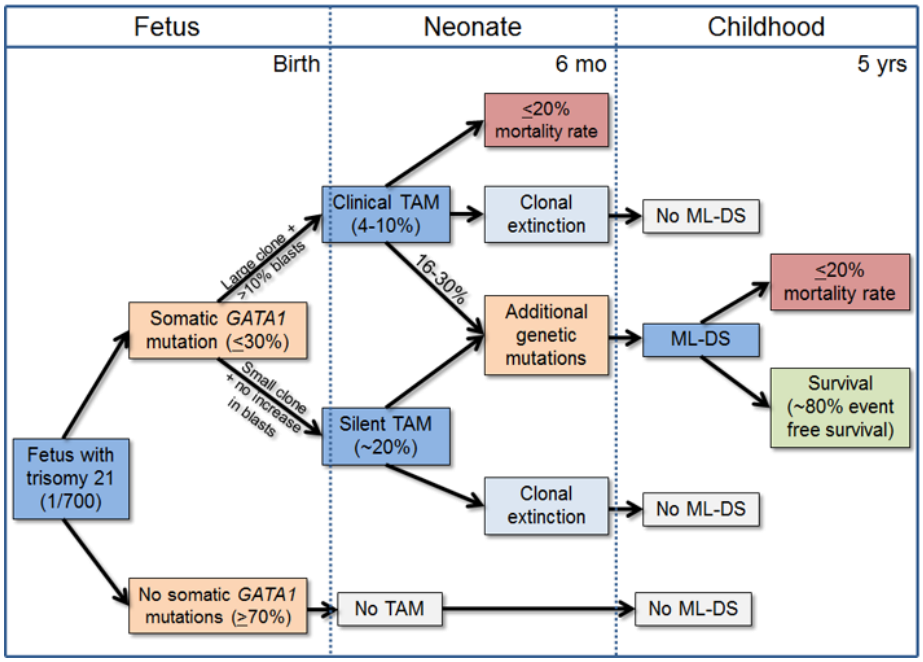


**Figure 1:** Natural history of transient abnormal myelopoiesis (TAM) and myeloid leukemia of Down syndrome (ML-DS) with approximate incidences of those affected. Both trisomy 21 and a somatic GATA1 mutation are required for progression to TAM. Most infants with TAM demonstrate extinction of the GATA1 clone; however, a subset acquires additional genetic mutations, allowing the progression to ML-DS. Overall, approximately 0.5-3% of Down syndrome patients develop ML-DS. Figure adapted from Bhatnagar et al., 2016 and Mateos et al., 2015.

# Clinics and pathology

**Note**

While this review focuses on myeloid proliferations in Down syndrome, it should be noted that children with Down syndrome are also at an increased risk of acute lymphoblastic leukemia (ALL), predominantly B lymphoblastic leukemia. The incidence of ALL in Down syndrome children younger than 5 years is 40.7 times higher compared to non-Down syndrome patients of the same age (Hasle et al., 2000). These Down syndrome-associated B-ALL have similar clinical features and cytogenetic abnormalities to B-ALL not associated with Down syndrome, though many more B-ALL associated with Down syndrome had normal karyotypes, except for their constitutional trisomy 21 (Forestier et al., 2008; Buitenkamp et al., 2014). However, these lymphoblastic leukemias are more frequently found to have overexpression of CRLF2, IKZF1 deletions, and/or JAK2 -activating mutations (Hertzberg et al., 2010; reviewed in Maloney et al., 2015). Down syndrome-associated ALL has a worse prognosis and overall event-free survival compared to non-Down syndrome-associated ALL due to increased treatment-related mortality and a higher relapse rate (Buitenkamp et al., 2014; reviewed in Maloney et al., 2015).

## Disease

**Transient abnormal myelopoiesis**

Transient abnormal myelopoiesis (TAM) is restricted to newborns with trisomy 21 or those with trisomy 21 mosaicism. The disease is characterized by increased peripheral blood blasts, usually megakaryoblasts, with or without clinical symptoms. Underlying genetics demonstrate somatic mutations in the GATA1 gene. Most cases spontaneously resolve within months without any therapeutic intervention.

## Phenotype/cell stem origin

The cell of origin is thought to be the fetal liver hematopoietic stem cell/progenitor cell.

## Etiology

The current hypothesis is that TAM arises in the liver. Evidence supporting this hypothesis includes the spontaneous resolution of hematopoiesis in the fetal liver within months of birth as hematopoiesis fully switches to the bone marrow, which is similar to the time course of TAM. In addition, severe TAM demonstrates increased blast infiltration of the liver with relative sparing of the bone marrow. Lastly, transgenic mice expressing GATA1 mutations show altered megakaryocyte lineage proliferation/differentiation only in fetal liver progenitors (reviewed in Roy et al., 2009). Evidence demonstrates that the presence of trisomy 21 promotes abnormal megakaryocyte-erythroid proliferation in the fetal liver (Chou et al., 2008; Tunstall-Pedoe et al., 2008). The addition of a somatic GATA1 mutation transforms the progenitors, leading to TAM. The combination of

constitutional trisomy 21 with somatic GATA1 mutations has been found to be both necessary and sufficient for TAM (Nikolaev et al., 2013).

## Epidemiology

As stated previously, TAM is restricted to newborns with trisomy 21, which has an incidence of approximately 1/700 live births. Clinical TAM (i.e. those with obviously increased blasts with or without symptoms) occurs in approximately 4-10% of those with trisomy 21. Approximately 5-16% of those affected with TAM have trisomy 21 mosaicism (Klusmann et al., 2008; Gamis et al., 2011). GATA1 mutations have been identified in 3.8% up to 30% of neonates with Down syndrome (Pine SR et al., 2007; Roberts et al., 2013). In a recent study using targeted next-generation sequencing of all Down syndrome neonates, low abundance GATA1 mutant clones were detected in 20.4% of neonates who were originally negative for mutations by Sanger sequencing/denaturing high performance liquid chromatography and thought to not have TAM (Roberts et al., 2013); the disease associated with these low level GATA1 mutation clones has been termed "silent TAM" due to their indistinguishable clinical picture and laboratory values compared to Down syndrome infants without TAM, including <10% blasts.

## Clinics

The clinical presentation of TAM is variable, with many infants (10-25%) being asymptomatic, only presenting with increased circulating blasts (Massey et al., 2006; Klusmann et al., 2008). While there is no defined percentage of blasts for the diagnosis of TAM, a threshold of >10% blasts has recently been found to have 100% sensitivity for detecting a coexisting GATA1 mutation, though the specificity is only 74% (Roberts et al., 2013). This specificity is low because, in general, Down syndrome neonates have increased peripheral blood blasts (median 4%; Roberts et al., 2013). Others recommend a blast minimum percentage of 20% (reviewed in Roberts and Izraeli, 2014). Of note, those with "silent TAM" do not have increased blasts compared to Down syndrome neonates without TAM.

The median presentation is within 3-7 days of birth. There is a slight male predominance with a male:female ratio of 1.2-1.5:1 (Massey et al., 2006; Klusmann et al., 2008). Peripheral blood evaluation also usually demonstrates a leukocytosis and an abnormal platelet count (usually thrombocytopenia, but thrombocytosis has also been identified); hemoglobin and absolute neutrophil counts are usually within normal limits. Of note, Down syndrome neonates without a diagnosis of clinical or silent TAM also often have similar peripheral blood abnormalities, so no individual finding other than increased blasts >10% is sensitive for a diagnosis of clinical TAM.

The most common clinical symptom is hepatomegaly, which is a result of megakaryoblast infiltration and/or hepatic fibrosis. This fibrosis is thought to be due to overexpression of platelet-derived growth factor and transforming growth factor-β ( TGFB1)by megakaryoblasts, and portends a poor prognosis (Klusmann et al., 2008). Other clinical findings include splenomegaly, exudative effusions (including pleural, pericardial, and ascites), and respiratory distress (due to hepatomegaly). Clinically severe TAM including these aforementioned symptoms occurs in approximately 10-30% of patients with clinically diagnosed TAM (reviewed in Roberts and Izraeli, 2014). In utero presentations include hydrops fetalis and anemia.

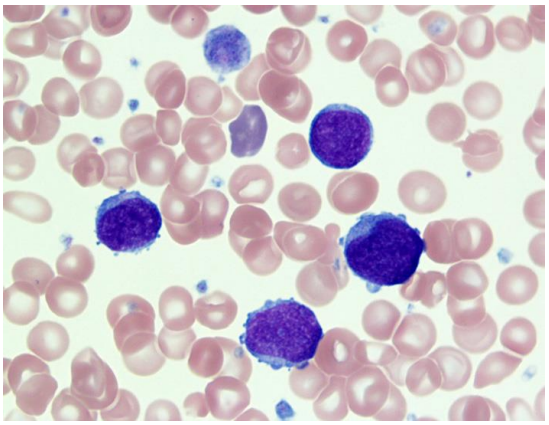

**Figure 2:** Peripheral blood smear reveals increased blasts which are medium to large in size with smooth chromatin, prominent nucleoli (sometimes multiple) and basophilic cytoplasm. Some of these blasts may demonstrate cytoplasmic blebs. Giant platelets may often be seen.

## Cytology

Blasts are characterized as medium to large cells with high nuclear-to-cytoplasmic ratios, smooth chromatin, prominent nucleoli, and deeply basophilic cytoplasm, often with cytoplasmic blebs. Cytoplasmic azurophilic granules may be identified.

## Pathology

Usually a bone marrow aspirate and/or biopsy does not need to be performed as the peripheral blood blast count is equal to or exceeds the bone marrow blast percentage. If performed, the bone marrow may demonstrate variable numbers of megakaryocytes, including frequent dysplastic forms such as micromegakaryocytes. Variable numbers of blasts may be present, in one study ranging from 0-87%, with a mean of 26% (Massey et al., 2006). Dyserythropoiesis may be seen in up to 25% of patients (Massey et al., 2006). Liver biopsies may demonstrate fibrosis with sinusoidal infiltration by megakaryoblasts (Massey et al., 2006).

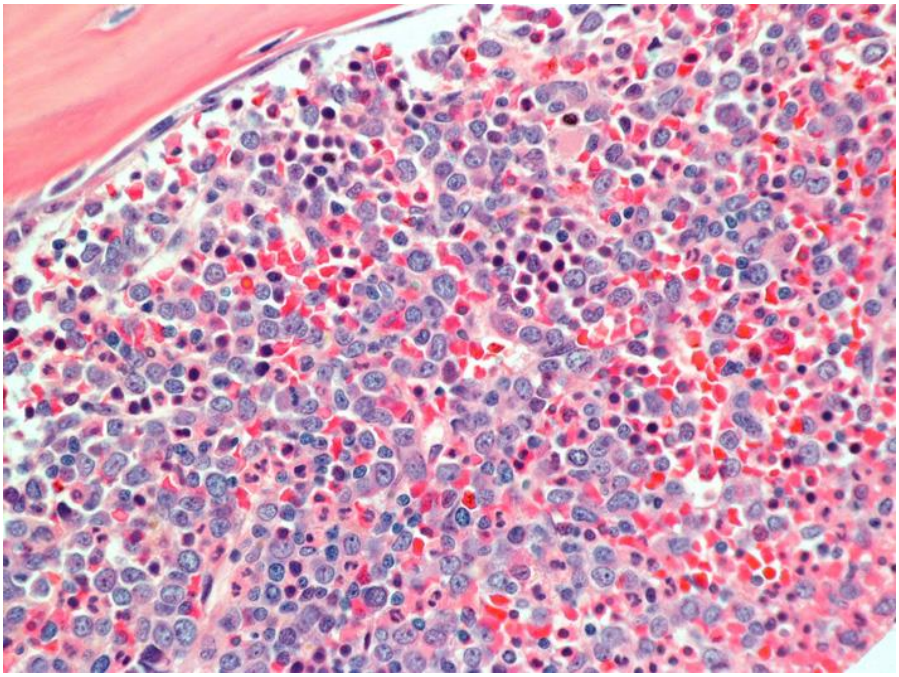

**Figure 3:** Bone marrow biopsy from a patient with TAM demonstrates increased blasts characterized as large cells with round to irregular nuclear contours, prominent nuclei, and mild amounts of cytoplasm. Background maturing erythroid and myeloid precursors are identified.

## Cytogenetics

Cytogenetics performed on peripheral blood most often demonstrates only trisomy 21 (Massey et al., 2006). However, approximately 20% of affected infants have additional cytogenetic aberrations including MLL gene rearrangements and complex karyotypes (Klusmann et al., 2008).

## Genes

TAM is characterized by somatic mutations in the transcription factor gene GATA1 on chromosome Xp11.23. These mutations are predominantly within exon 2 (97%), with the remaining identified mostly in exon 3.1 (Alford et al., 2011). GATA1 mutations result in N-terminal truncating mutations leading to a shortened GATA1 protein, GATA1s. Of note, 10-20% of cases of TAM have multiple GATA1 mutant clones (Alford et al., 2011; Roberts et al., 2013). Whole exome sequencing of TAM cases has reveal low numbers of non-silent mutations in other genes in these patients (1.7, range 1-5; Yoshida et al., 2013). However, Nikolaev et al. (2013) found that the presence of such additional mutations can accumulate in TAM without immediate progression to ML-DS, and that these individuals with additional mutations can still have disease regression.

## Treatment

Approximately 66-84% of infants will have spontaneous resolution of their blasts and symptoms without a need for intervention (Klusmann et al., 2008; Gamis et al., 2011). The remaining infants may need supportive therapy or chemotherapy. In previous trials, supportive care measures including exchange transfusions and/or leukapheresis were provided for hyperviscosity, blast counts >100K/uL, organomegaly with respiratory compromise, heart failure, hydrops fetalis, liver dysfunction, and disseminated intravascular coagulation (DIC) (Gamis et al., 2011). Even more severe life-threatening symptoms have been treated successfully with cytarabine (cytosine arabinose), to which the blasts are highly sensitive (Massey et al., 2006).

## Evolution

The majority of patients (66-84%) have spontaneous resolution of clinical and laboratory abnormalities without treatment within 2-3 months (Klusmann et al., 2008). Peripheral blasts usually clear prior to hepatomegaly resolution (Gamis et al., 2011). Approximately 16-30% of infants, whether they were asymptomatic or had clinical symptoms,

develop myeloid leukemia of Down syndrome (Klusmann et al., 2008) (see below).

## Prognosis

While most infants have spontaneous resolution, approximately 15-20% of infants still die; however, approximately half of these deaths are not TAM-related, but instead related to other congenital abnormalities of trisomy 21 (Klusmann et al., 2008; Gamis et al., 2011). TAM mortality risk factors include WBC >100 K/uL, prematurity, ascites, effusions, bleeding diathesis/ coagulopathy, and failure to spontaneously clear peripheral blasts (Klusmann et al., 2008). Those with pathologically diagnosed hepatic fibrosis are more likely to die of disease (Gamis et al., 2011).

## Disease

**Myeloid leukemia of Down syndrome**

**Note**

Myeloid leukemia of Down syndrome (ML-DS) encompasses a spectrum of myelodysplastic syndrome and its evolution into leukemia in children with Down syndrome.

## Etiology

Similar to TAM, trisomy 21 and a somatic GATA1 mutation are thought to be required for the development of ML-DS. However, for this progression, additional genetic and/or epigenetic events are required. Children over 5 years old may not have mutations in the GATA1 gene, and possible consideration should be given to a more conventional MDS or AML similar to those diagnosed in non-Down syndrome patients; these children may need therapy with appropriate non-Down syndrome protocols.

In those under 5 years of age, most cases of ML-DS (~70%) are acute megakaryoblastic leukemia (AML M7 by French-American-British (FAB) categorization) (Gamis et al, 2003). Occasional presentations of FAB M0, M1, M2, and M4/M5 have also been reported (Lange et al., 1998; Rao et al., 2006).

## Epidemiology

The incidence of acute myeloid leukemia in individuals with Down syndrome is 0.5-3%, up to 150 times greater than that in individuals without Down syndrome of the same age; the incidence of acute megakaryoblastic leukemia in individuals with Down syndrome is up to 500 times greater than that in individuals without Down syndrome (Creutzig et al., 1996; Hasle et al., 2000). ML-DS usually presents between 1-4 years of age (median 1.5 years) (Klusmann et al., 2008). This disease develops in approximately 16-30% of children with a clinical history of TAM. However, when taking into account those with "silent TAM", the risk of developing ML-DS is approximately 5-11% (Roberts et al., 2013). At this time, there are no specific clinical, laboratory, or molecular features that predict the risk of TAM transforming into ML-DS. Similarly, whether an individual receives treatment for TAM has not been correlated with the progression to ML-DS.

Of note, GATA1 gene mutation testing/monitoring is not currently the standard of care in patients with Down syndrome. Many groups advocate for a peripheral blood smear with differential at birth and every three months thereafter until the age of 4 years, at which time the risk of leukemia is reduced (Roy et al., 2009; Mateos et al., 2015; Bhatnagar et al., 2016).

## Clinics

ML-DS may occur after a remission time period from TAM, or as an overt progression/evolution of TAM without a period of remission. In the latter, the infant may have persistent abnormal laboratory values over several months, and in the former, the laboratory values tend to normalize. In those with silent TAM or in remission, ML-DS is usually first detected by thrombocytopenia with or without leukopenia and anemia and with low numbers or absent circulating blasts (Lange et al., 1998). In approximately 70% of patients, myelodysplastic syndrome precedes acute leukemia (Creutzig et al., 1996). Hepatosplenomegaly may be present. Compared to non-Down syndrome cases of myeloid leukemia, ML-DS cases are less likely to have lymphadenopathy and CNS blast involvement (Gamis et al., 2003).

## Cytology

Peripheral blood and bone marrow blasts in ML-DS are similar to those in TAM, both morphologically and immunophenotypically. The bone marrow aspirate may be hemodilute and/or aparticulate due to marrow fibrosis hampering aspiration. During the myelodysplastic syndrome phase, dysplastic changes of megakaryocytes and erythroid cells may also be identified along with low levels of blasts in the bone marrow.

## Pathology

A bone marrow biopsy usually demonstrates progressive fibrosis. Blasts and dysplastic megakaryocytes are the predominant cells. The blasts have a similar immunophenotype to those in TAM, expressing CD34, CD117, CD13, CD33, CD36, CD71, variable CD41, variable CD42b, variable CD61, CD56, dim CD4, and aberrant expression of CD7 (Gamis et al., 2003); however, approximately 50% of cases do not express CD34, and 30% of cases do not express CD56 and CD41.

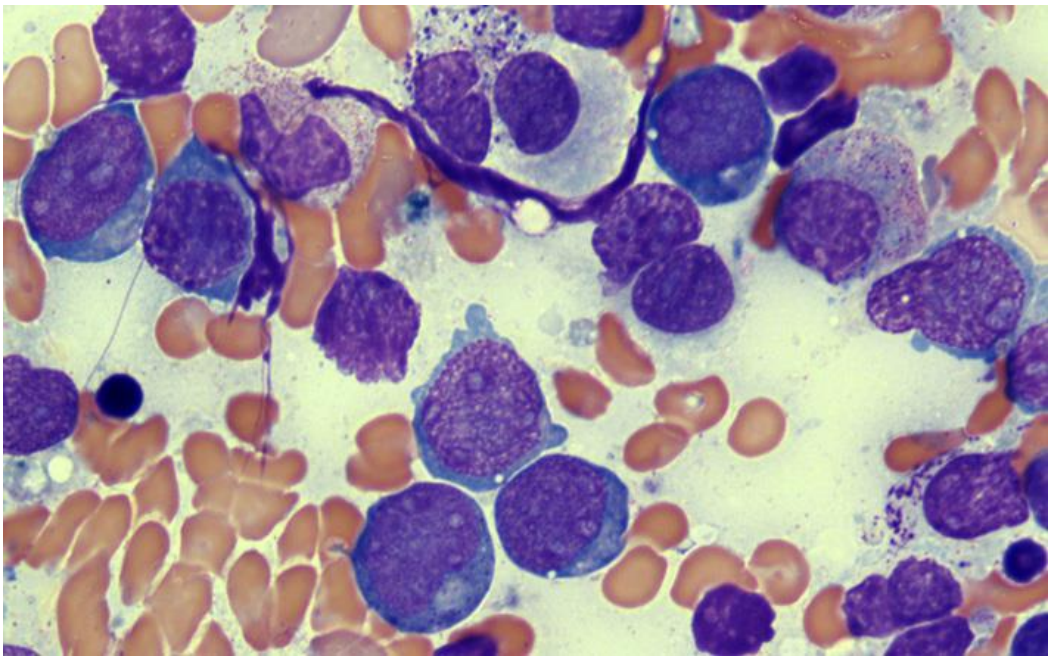

**Figure 4:** Increased blasts may be identified on a bone marrow aspirate if it does contain particles. These blasts are characterized as medium to large sized cells with round to irregular nuclear contours, smooth chromatin, prominent nucleoli (sometimes multiple), and basophilic cytoplasm often with cytoplasmic blebs. Rare blasts may demonstrate cytoplasmic granules such as the blast in the bottom center. Dysplastic megakaryocytes may also be identified such as the small megakaryocyte at the top center.

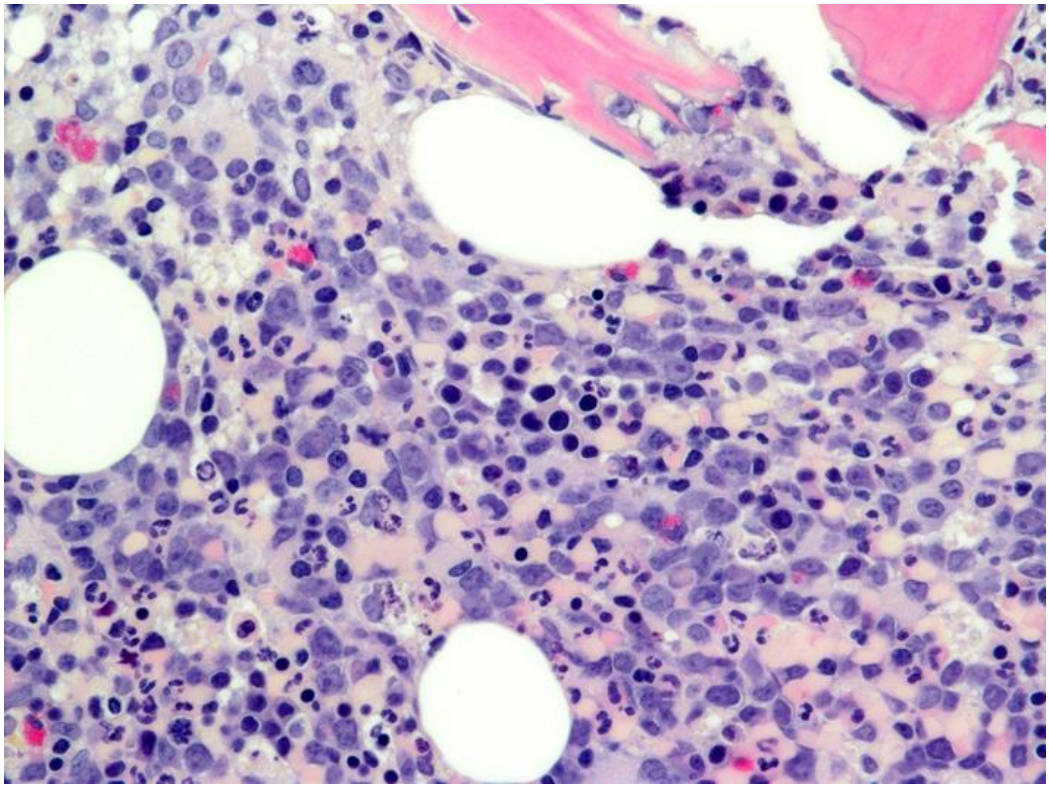

**Figure 5:** In the bone marrow biopsy obtained from the same patient demonstrated in Figure 4, the core biopsy demonstrates increased blasts with prominent nucleoli in a background of maturing erythroid and myeloid precursors.

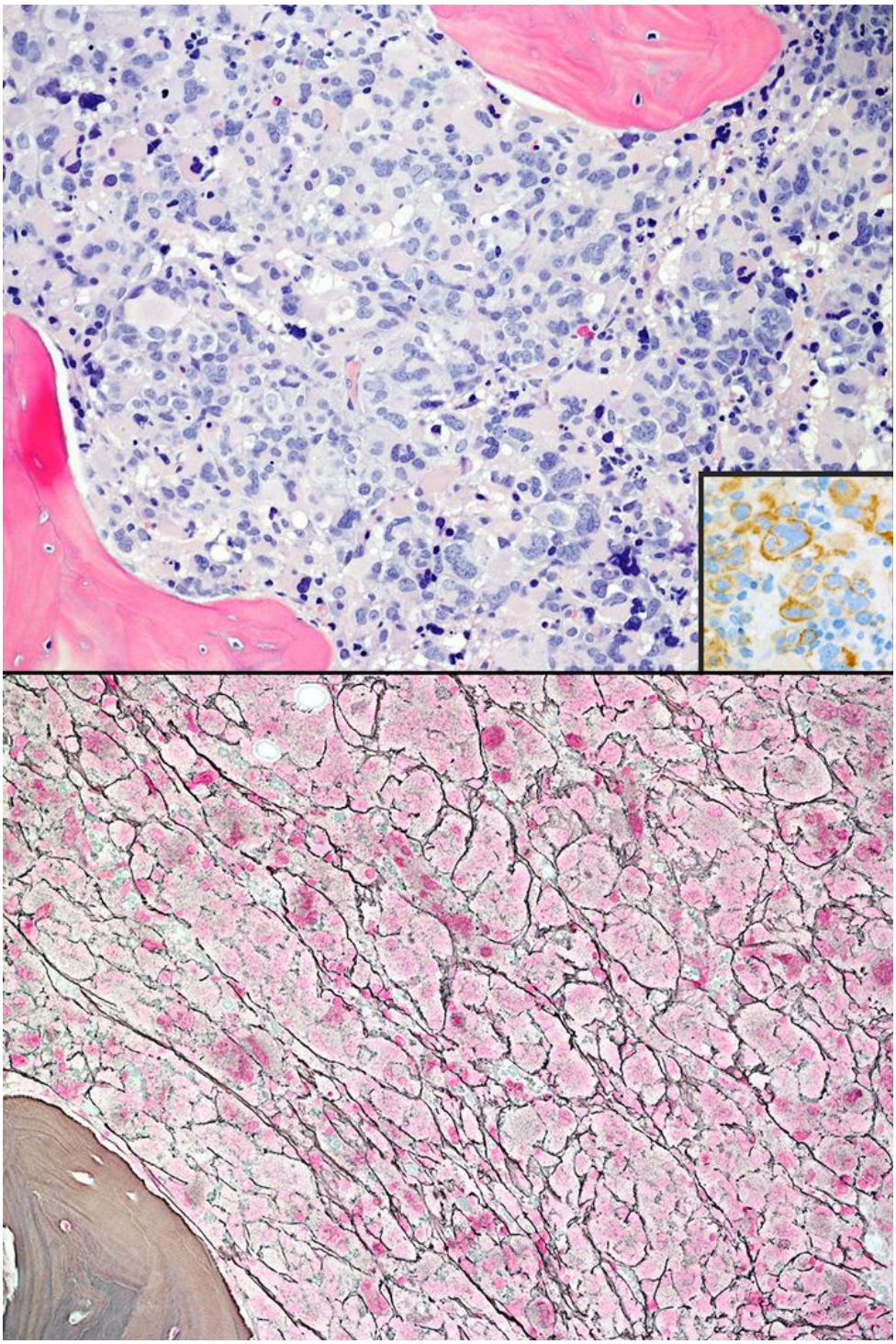

**Figure 6:** Other bone marrow biopsies may demonstrate marked fibrosis, as demonstrated by the bottom panel stained for reticulin. The core biopsy can demonstrate a marked increase in atypical and dysplastic megakaryocytes, many of which are blasts. The inset panel demonstrates CD117 immunohistochemical staining of the megakaryoblasts.

## *Cytogenetics*

Karyotypes in ML-DS often demonstrate only the constitutional trisomy 21 (25-29% of cases) (Lange et al., 1998; Blink et al., 2014). Recurrent genetic abnormalities such as t(8;21), t(15;17), and inv(16) are underrepresented in this cohort compared to those without Down syndrome. The translocation t(1;22) often found in infant megakaryoblastic leukemia is only rarely found in ML-DS. However, trisomy 8 is a common cytogenetic abnormality, occurring in 13-36% of patients, as is an additional nonconstitutional chromosome 21 (Creutzig et al.,

1996; Lange et al., 1998; Gamis et al., 2003; Blink et al., 2014). Loss of chromosome 5 and/or loss of chromosome 7 material is present in 23% of cases (Blink et al., 2014).

### Genes

N-terminal somatic mutations in the GATA1 gene are present in all cases of ML-DS, and, usually, an individual has the same GATA1 clone in both TAM and ML-DS. However, 10-20% of cases of TAM have multiple GATA1 mutant clones, and the larger size of the GATA1 mutant clone has not been found to always correspond with the clone present in ML-DS (Nikolaev et al., 2013; Yoshida et al., 2013). By whole exome sequencing, more non-silent mutations in additional genes are present in ML-DS compared to TAM, with recurrent mutations identified in core cohesion components (including RAD21 and STAG2), CTCF, epigenetic regulators (including EZH2 and KANSL1), RAS pathway genes (including NRAS, JAK1, and JAK2), and other genes (including DCAF7 and TP53) (Yoshida et al., 2013).

### Treatment

Unlike TAM, ML-DS does require chemotherapy to achieve complete remission (CR). However, compared to non-Down syndrome pediatric acute leukemia, they can be treated with reduced intensity chemotherapy protocols without stem cell transplantation. Reduced chemotherapy intensity is encouraged due to high rates of treatment toxicity in Down syndrome children (Lange et al., 1998).

### Prognosis

Unlike non-Down syndrome myeloid leukemia, ML-DS has a better prognosis, with better induction remission rates and reduced relapse rates (Lange et al., 1998; Gamis et al., 2003; Rao et al., 2006). Blink et al. (2014) reported a 7-year event-free and overall survival rate of 78% and 79%, respectively. However, ML-DS children are still at high risk for treatment-related deaths, often due to infection (Lange et al., 1998; Rao et al., 2006). White blood count >20K/uL and age >3 years are independent predictors for poor event-free survival (Blink et al., 2014). In another study, age >2 years was correlated with a five fold increase in adverse outcomes (Gamis et al., 2003). A normal karyotype (except for the constitutional trisomy 21) has also been found to independently predict inferior overall survival, event-free survival, and relapse-free survival (Blink et al., 2014).

## Genes involved and proteins

### GATA1 (GATA binding protein 1 (globin transcription factor1))

**Location**

Xp11.23

**Protein**

GATA1 protein is a transcription factor which regulates megakaryocytes and erythroid differentiation.

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