Myeloid Proliferations of Down Syndrome

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Individuals with Down syndrome (DS) have a markedly increased risk of developing unique myeloid proliferations such as transient abnormal myelopoiesis (TAM) and myeloid leukemia associated with Down syndrome (ML-DS) [1, 2]. These proliferations occur in the first 3 years of life and are a result of several transforming genetic events that arise during the fetal and newborn period. The initial event, an additional chromosome 21, leads to increased megakaryocytic proliferation in the fetal liver. Subsequent mutation of *GATA*-binding protein *1* (*GATA1*) results in the development of TAM. Further acquisition of additional mutations of epigenetic regulators and common signaling pathways such as JAK family kinases, MPL, and multiple RAS pathway genes leads to the transformation to ML-DS [3].

While the time of presentation varies, TAM typically occurs shortly after birth, whereas ML-DS typically occurs between 3 months and 3 years of age. The morphologic and immunophenotypic features of the myeloid proliferations of DS are essentially indistinguishable, (Table 12.1, Figs. 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 12.10, and 12.11).

Approximately 4% to 18% of individuals with DS develop TAM, although the true incidence of TAM is difficult to discern in view of the fact that most infants are asymptomatic, so blood counts or morphologic evaluation may not be performed [4]. TAM typically occurs at the time of birth (or within the first few days following birth) and is defined as an increase in peripheral blasts that have morphologic and phenotypic features of megakaryocytic lineage. There is no internationally agreed-upon definition of a percentage blast threshold for diagnosis, however, and circulating blasts are also frequently seen in DS individuals without TAM. The blasts in TAM harbor acquired N-terminal truncating mutations in the key hematopoietic transcription factor gene *GATA1* [5, 6]; this mutation is considered a molecular hallmark of these disorders. A subset of patients with so-called silent TAM may also have acquired *GATA1* mutations despite lacking clinical or overt hematologic manifestations of disease [7]. In most cases (75–90%), the peripheral blasts resolve spontaneously by approximately 3 months of age without the need for chemotherapy, although a few children may experience life-threatening or even fatal complications.

Approximately 20% of patients with clinically apparent TAM subsequently develop nonremitting acute myeloid leukemia (AML), when persistent *GATA1*-mutant cells acquire additional oncogenic mutations [8–12]. ML-DS encompasses cases of both myelodysplastic syndrome (MDS) and overt AML, which behave in a similar fashion regardless of the absolute blast count [1]. ML-DS occurs later than TAM, usually in the first 3 years of life, and is usually preceded by TAM. In most cases, the acute leukemia is a megakaryoblastic leukemia, in contrast to the relatively low incidence of this leukemia in non-DS individuals. ML-DS has a relatively favorable prognosis with enhanced chemotherapeutic responsiveness.

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Table 12.1 The myeloid proliferations of Down syndrome

	Transient abnormal myelopoiesis (TAM)	Myeloid leukemia associated with Down syndrome (ML-DS)
Incidence in DS individuals	4–18%	1–2%
Onset	From birth to first few days of life; may also present in the fetal period	Usually <3 y (median age about 2 y)
Clinical features	Variable, ranging from asymptomatic (the majority) to disseminated leukemic infiltration; clinical manifestations may include hepatomegaly, jaundice, splenomegaly, pericardial/pleural effusions, and bleeding diatheses	Most cases have a history of preceding TAM and have an indolent presentation; organomegaly may be present
Laboratory features	Leukocytosis (30–50%) with peripheral blood blasts and granulocytic left shift; platelets may be increased, decreased, or normal (with large forms usually present); megakaryocyte fragments may be seen; significant anemia is uncommon, and marked polychromasia and circulating nucleated red cells may also be seen	Progressive pancytopenia with leukopenia, thrombocytopenia, and evidence of dysplasia; the circulating blast percentage is typically low
Immunophenotype	Variable, but usually involves expression of a combination of stem cell markers (CD34, CD117), myeloid markers (CD13, CD33), and platelet glycoproteins (CD36, CD41, CD61), with variable expression of CD4, CD7, and CD56; staining for nonspecific esterase is also usually positive and MPO is negative	
Molecular features	*GATA1* mutations present in all cases	*GATA1* mutations present in all cases; cytogenetic abnormalities include trisomy 8, trisomy 11, loss of chromosome 5 and 7 material, del(6q), del(7p), del(16q), and dup(1p); other mutations involve key cohesion component genes (*RAD21, STAG2, SMC3, SMC1A*), epigenetic regulators (*EZH2, KANSL1*), *CTCF*, RAS pathway genes, and somatic point mutations in *JAK1, JAK2, JAK3, PT53, FLT3,* and *MPL*
Prognosis	Most neonates (>80%) undergo spontaneous remission within 3–4 months; overall 5-year survival is 80%	Long-term survival has been reported, with outcomes better than non-DS AML (event-free survival of 80%); prognosis after relapse is poor

AML acute myeloid leukemia

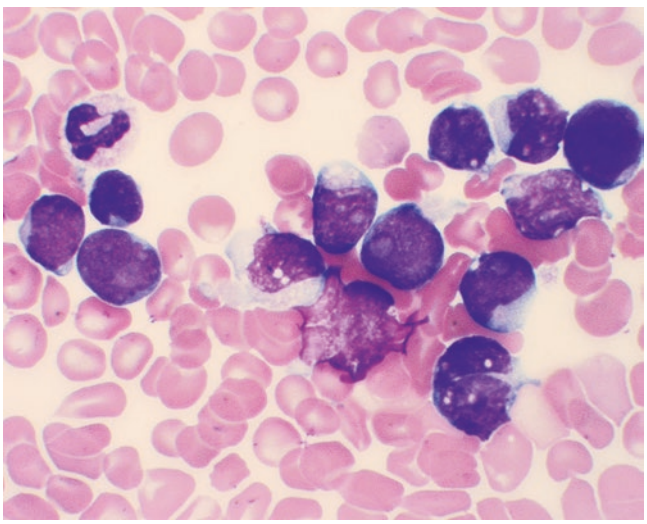

Fig. 12.1 The peripheral blood smear in transient abnormal myelopoiesis (TAM) typically shows leukocytosis, with increased blasts exhibiting megakaryoblastic morphology, although the morphology may be variable. The neoplastic cells characteristically show high N:C ratio, with fine chromatin and prominent nucleoli. The basophilic cytoplasm may be scant to moderate and may demonstrate occasional peripheral "blebs." Small vacuoles may also be present [Wright-Giemsa, 100×]

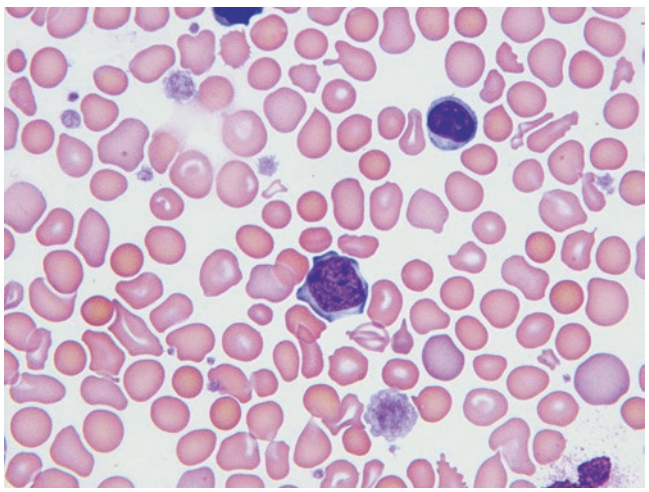

Fig. 12.2 The platelet count in TAM may be increased or decreased, and the peripheral blood smear may show numerous large platelets (pictured) in addition to megakaryocytic fragments. A circulating blast is also illustrated in the center of the image [Wright-Giemsa, 100×]

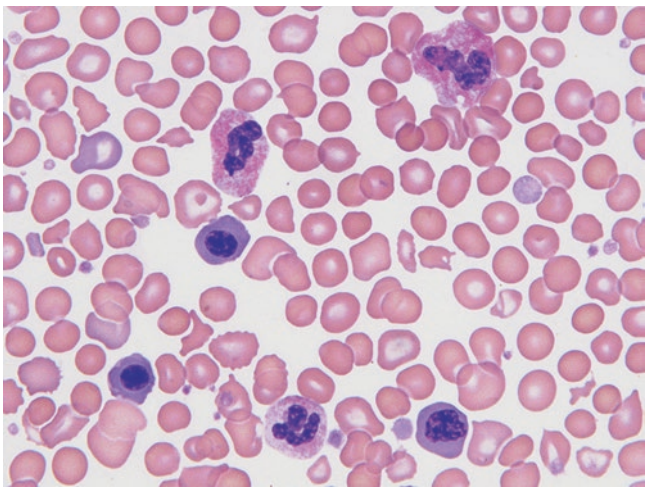

Fig. 12.3 Numerous polychromatophilic cells and circulating nucleated red cells are often seen in the peripheral blood in TAM. Other changes involving the red cells that may be seen in Down syndrome (in the absence of TAM) include an increase in the mean corpuscular hemoglobin (MCH) and mean cell volume (MCV), usually evident at 9 to 12 months of age [13, 14] [Wright-Giemsa, 100×]

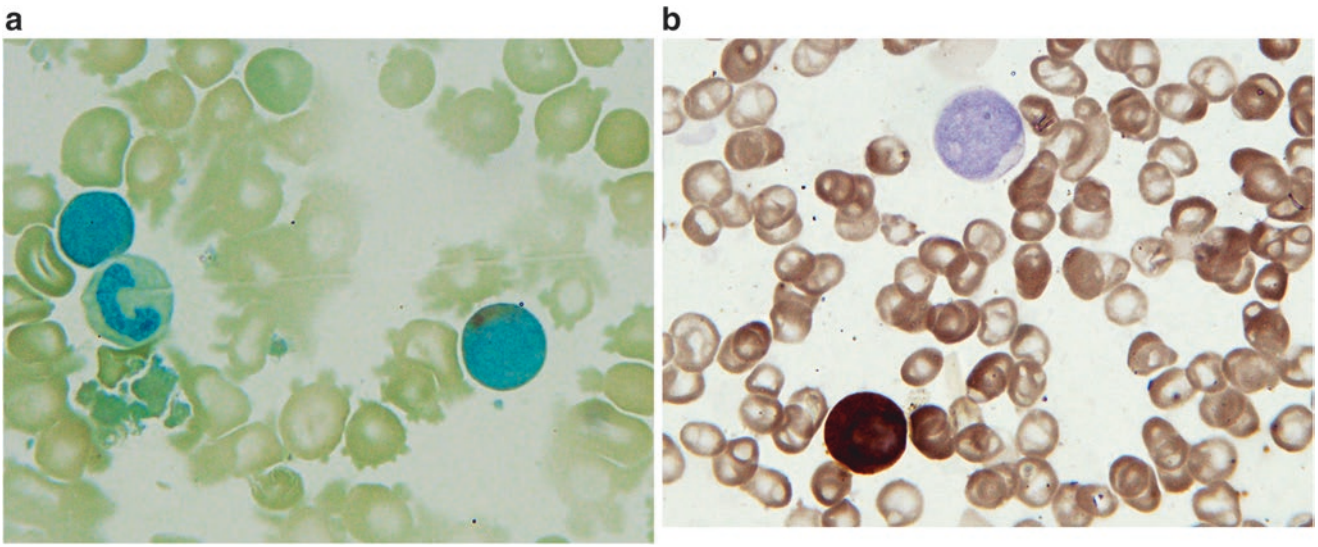

Fig. 12.4 The blasts in TAM are shown to be positive for nonspecific esterase (**a**) and negative for myeloperoxidase (**b**), with the latter showing strong positivity in an adjacent granulocyte precursor. Myeloperoxidase may show weak staining in some cases [nonspecific esterase and myeloperoxidase cytochemical stains, 100×]

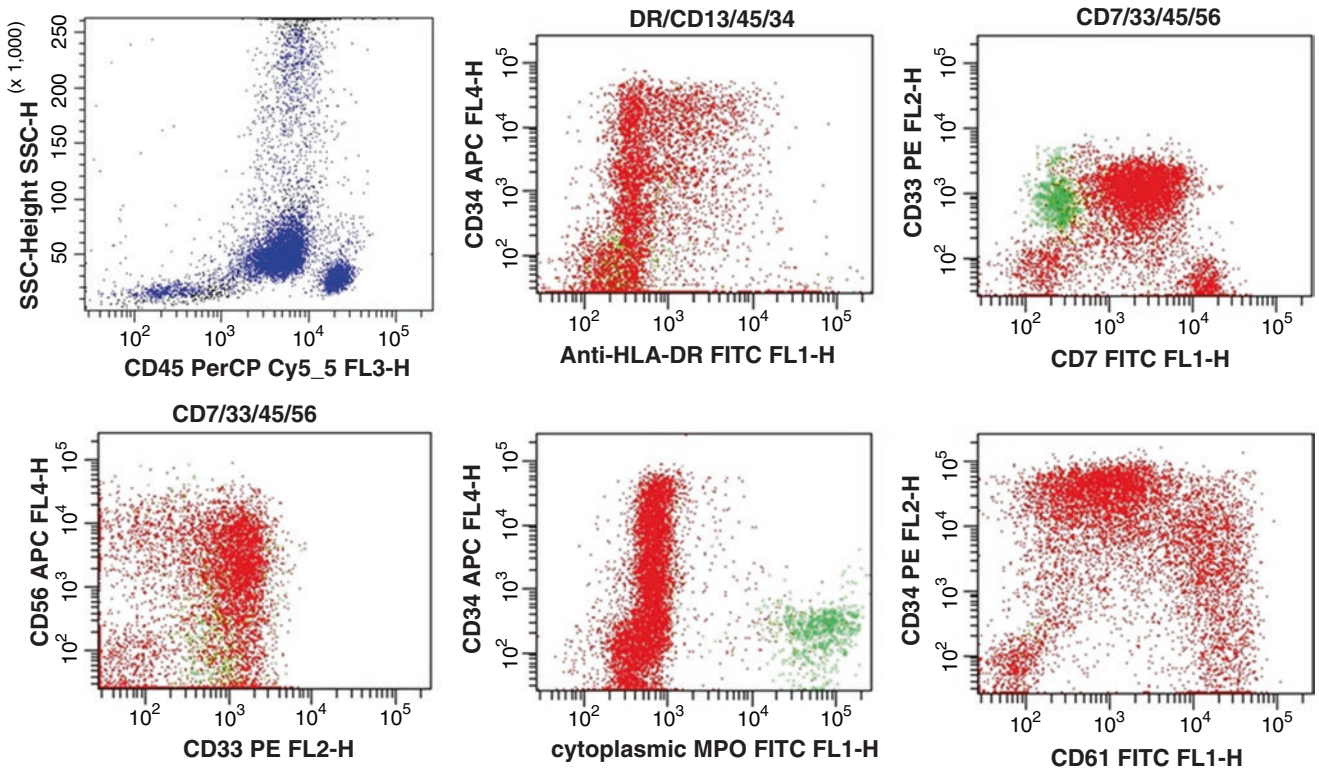

Fig. 12.5 By flow cytometry, the blasts in TAM show moderate to bright CD45 expression, in addition to expression of immature marker CD34, myeloid marker CD33, and megakaryocyte marker CD61. CD7 and CD56 are also aberrantly expressed on the blasts. HLA-DR and MPO are negative. The intensity of CD34 expression appears uniformly heterogeneous. Also demonstrated is a pattern of loss of CD34 expression with increasing expression of CD61 (bottom right plot), suggestive of "maturation" of the neoplastic cells. The phenotype is consistent overall with megakaryocytic differentiation

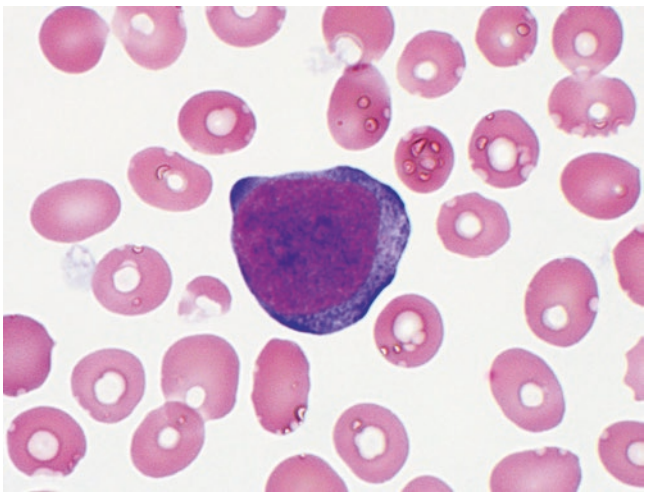

Fig. 12.6 The circulating blasts in myeloid leukemia associated with Down syndrome (ML-DS) also typically exhibit megakaryoblastic morphology, characterized by fine chromatin and prominent nucleoli. The cytoplasm is typically deeply basophilic and may show occasional cytoplasmic blebbing and vacuolation. The blasts usually circulate in relatively low numbers [Wright-Giemsa, 100×]

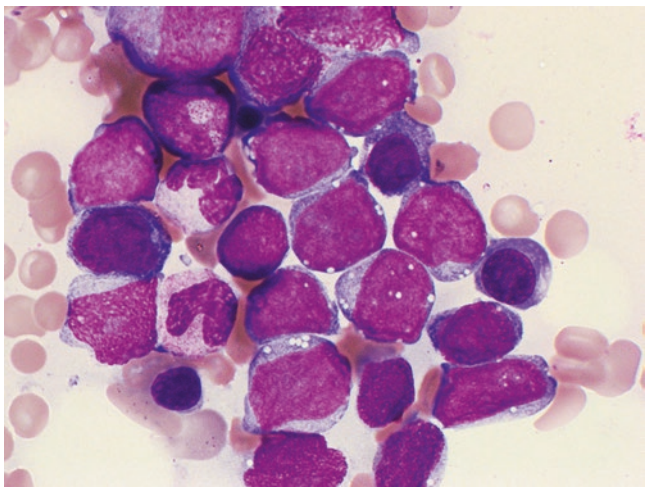

Fig. 12.7 The bone marrow aspirate in ML-DS shows increased numbers of megakaryoblasts, with relatively reduced background hematopoietic elements. In some instances, the presence of marked bone marrow fibrosis may produce a "dry tap" [Wright-Giemsa, 100×]

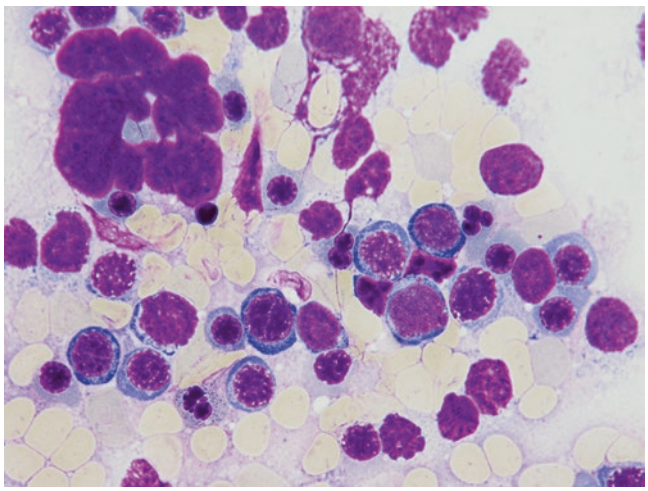

Fig. 12.8 There may be prominent dysplasia present in ML-DS, here shown to affect the red cell lineage in a bone marrow aspirate. Mature red cell precursors show multinucleation and nuclear budding [Wright-Giemsa, 100×]

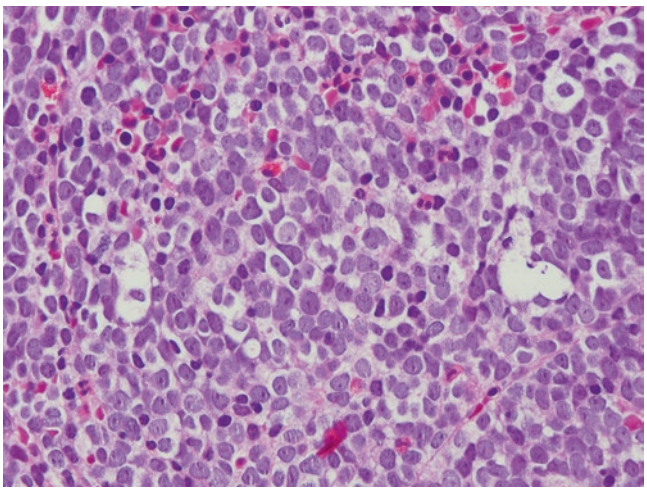

Fig. 12.9 The bone marrow core biopsy in acute megakaryoblastic leukemia typically shows a hypercellular bone marrow with sheets of blasts showing pale, fine chromatin, visible nucleoli, and variable amounts of cytoplasm. Background hematopoietic elements are reduced. Reticulin fibrosis may also be prominent in some cases (*not shown*) [H&E, 40×]

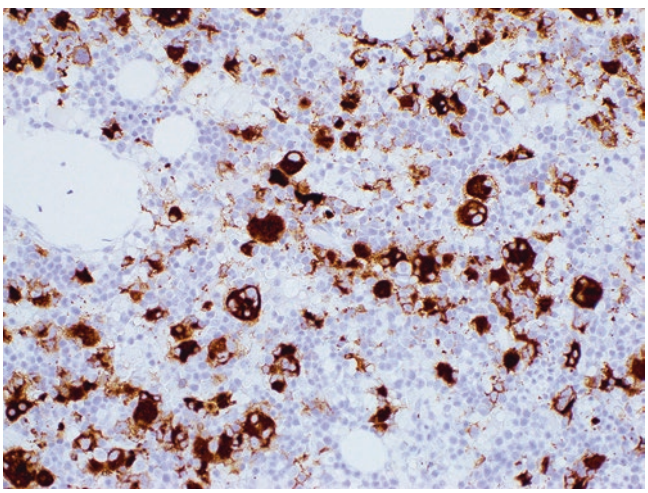

Fig. 12.10 The blasts in the bone marrow core biopsy in ML-DS can be highlighted by a CD61 immunostain, which also highlights occasional larger background megakaryocytes [CD61, 40×]

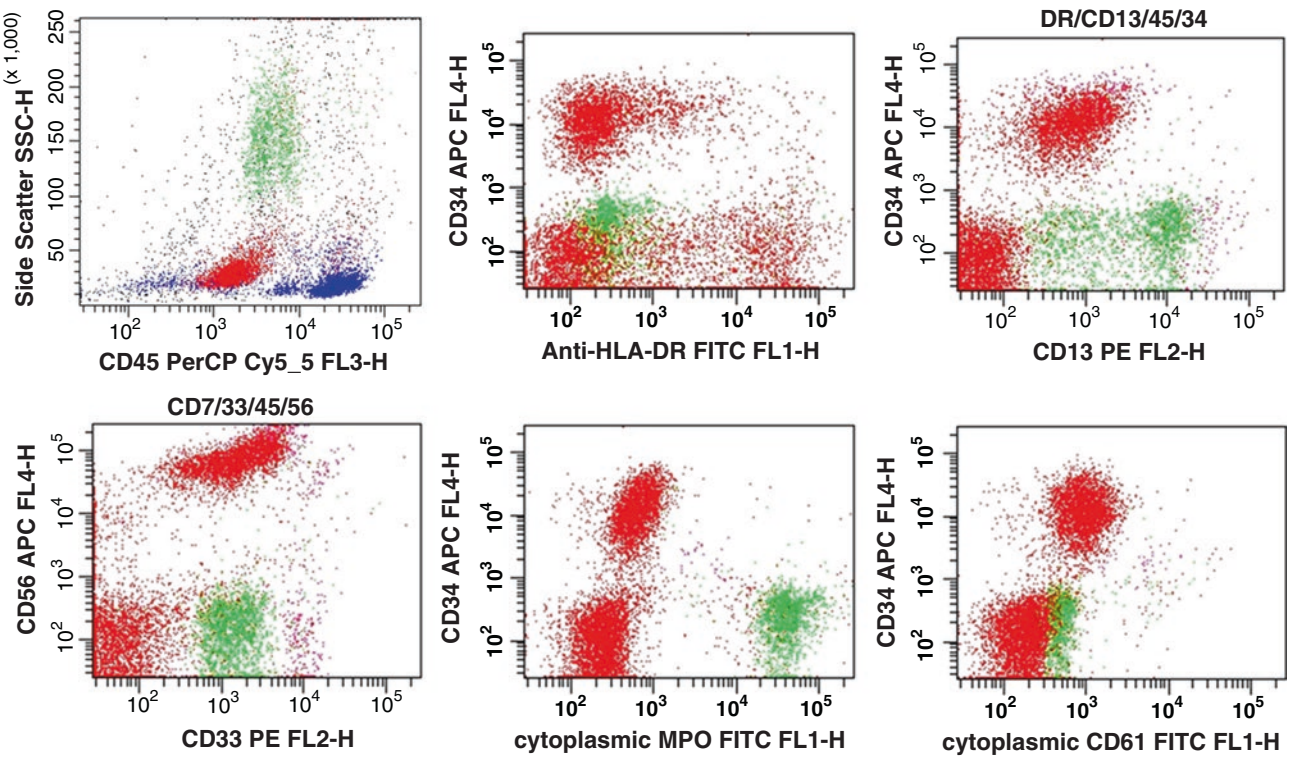

Fig. 12.11 The blasts in acute megakaryoblastic leukemia show a similar phenotype to that seen in TAM, here showing expression of immature marker CD34, myeloid markers CD13 and CD33, and megakaryocyte marker CD61. There is also bright aberrant expression of CD56. HLA-DR and MPO are negative. In contrast to TAM, the CD34 expression shown here is bright, with a more discrete population showing relatively little heterogeneity. Furthermore, there does not appear to be the same "phenotypic" maturation pattern (i.e., loss of CD34 with increasing CD61 expression) as illustrated previously in the case of TAM (Fig. 12.5)

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