Monosomy 7 in Pediatric Myelodysplastic Syndromes

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KEYWORDS

• Monosomy 7 • GATA2 • SAMD9L • SAMD9 • Pediatric MDS

KEY POINTS

- Complete (monosomy 7) or partial (del7q) loss of chromosome 7 is the most common cytogenetic aberration in pediatric myelodysplastic syndromes (MDS).
- Most children with primary MDS and chromosome 7 loss carry an underlying genetic defect: GATA2 deficiency or SAMD9/SAMD9L disease.
- In patients with germline SAMD9/SAMD9L mutations, the evolution of monosomy 7 or del7q is nonrandom and selects for clones retaining wild-type alleles.
- MDS with monosomy 7 is associated with a high risk of clonal progression and therefore necessitates early hematopoietic stem cell transplantation.

INTRODUCTION

Pediatric myelodysplastic syndromes (MDS) are a rare group of clonal hematopoietic stem cell (HSC) disorders accounting for less than 5% of hematopoietic neoplasia in childhood. The main hallmarks are morphologic dysplasia, ineffective hematopoiesis, and PB cytopenias.[1] The first World Health Organization (WHO) classification for pediatric MDS in 2001 recognized the categories of refractory cytopenia of childhood (RCC) characterized by peripheral blood (PB) blasts less than 2% and bone marrow (BM) blasts less than 5%, refractory anemia with excess blasts (RAEB) with PB blasts 2% to 19% and/or BM blasts 5% to 19%, and RAEB in transformation (RAEB-T) with PB and/or BM blasts 20% to 29%.[1] This straightforward approach was incorporated into the next WHO classification in 2008.[2] In the latest WHO classification from 2016, the criteria for RCC remained the same; however, MDS with excess of blasts is now referred to as MDS-EB and would encompass both pediatric categories RAEB and RAEB-T.[3]

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There are several important differences between pediatric and adult MDS. In children, the findings of ringed sideroblasts or del(5q) cytogenetic aberration are exceedingly rare; instead, loss of chromosome 7 is the most common cytogenetic aberration. Although anemia is frequently the main initial symptom in adults with MDS, thrombocytopenia and neutropenia are more prominent in children.[4] The somatic mutational landscape also differs according to the age at diagnosis. The typical adult-type mutations in *TET2*, *DNMT3A*, and the spliceosome complex are generally not present in children. Instead, somatic driver mutations in *SETBP1*, *ASXL1*, *RUNX1*, and the *RAS* oncogenes define the clonal mutational landscape in pediatric MDS.[5,6]

MDS secondary to chemo- or radiation therapy differs in biology, clinical course and outcome from MDS developing in the presence of a preceding classical inherited bone marrow failure syndrome (IBMFS) such as Fanconi anemia (FA) or severe congenital neutropenia (SCN), or MDS with prior acquired aplastic anemia (AA). All other cases of MDS are conventionally referred to as "primary" MDS, although it has to be assumed that these cases have an underlying yet unknown predisposition. In fact, the recently reported MDS predisposition syndromes GATA2 deficiency and SAMD9/SAMD9L diseases account for a considerable proportion of these cases in pediatric cohorts. Monosomy 7 and partial deletion of the long arm of chromosome 7 (del7q) are common cytogenetic lesions encountered across all ages in myeloid malignancies.[7] The heterogeneous nature and rapid clonal progression of −7 MDS pose a challenge to clinical management.

In this article, the authors provide a summary of their understanding of pediatric MDS with monosomy 7, with a specific focus on MDS predisposition syndromes associated with monosomy 7.

FREQUENCY OF MONOSOMY 7 IN PEDIATRIC MYELODYSPLASTIC SYNDROMES

Among patients with loss of chromosome 7 aberrations, a complete loss of one copy of chromosome 7 (monosomy 7, -7) accounts for the majority of cases. Some patients may however acquire only a partial deletion of genomic material on 7q (del7q), or the unbalanced translocation der(1;7)(q10;p10), resulting in monosomy for 7q. For clarity, all aforementioned cytogenetic aberrations are referred to as monosomy 7 or −7 in this article. Isochromosome 7q [i (7)(q10)] is a rare and nonrandom cytogenetic aberration that is fairly specific to patients with Shwachman-Diamond syndrome (SDS).[8] Although karyotypes involving −7 are very common in pediatric MDS, they are generally rare in pediatric patients with acute myeloid leukemia (AML), accounting for less than 5% of cases.[9]

Primary Myelodysplastic Syndromes

The overall incidence of monosomy 7 in pediatric MDS can be assessed from several studies investigating heterogenous patient cohorts. Within primary MDS (combining both RCC and MDS-EB), monosomy 7 occurs in up to ~20% of patients.[4,10,11] RCC is the most common subtype of pediatric MDS (>2/3 of cases). Most RCC patients (~80%) have hypocellular marrow, and in this patient group, monosomy 7 is found in 9% of cases. In the remaining ~20% of RCC patients with normal or increased cellularity, the incidence of monosomy 7 increases to 19%.[1] Among patients with MDS predisposition syndromes, a strong association can be seen with GATA2 deficiency and SAMD9/SAMD9L disorders.[6,10] As of today, it can be assumed that both genetic syndromes explain the hereditary cause in at least half of patients with "primary" pediatric MDS and −7 (**Fig. 1**). These syndromes are discussed in detail in the later discussion. Monosomy 7 has also been reported, albeit at considerably lower frequencies in MDS arising from germline *RUNX1* and *ERCC6L2* mutations.[12,13]