Pediatric MDS with a germline GATA2 heterozygous deletion, monosomy 7, and somatic CRLF2 mutation

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Choladda V. Curry, M.D.

Kevin E. Fisher, M.D., Ph.D.
Clinical History

12 year old male, previously healthy, presented with fever, cough, and diagnosed with pneumonia.

CBC: WBC 1.9 K/uL, Hgb 9.4 g/dL, Hct 27.3%, RBC 2.77 M/uL, MCV 98.6 fL, MCH 33.9 pg, MCHC 34.4 g/dL, RDWCV 15.3%, plt 409 K/uL, ANC 0.79 K/uL, AMC 0.11 K/uL, ALC 0.93 K/uL and 1.6% blasts.
Fig 2: At diagnosis, bone marrow aspirates with dysplastic megakaryocytes.
Fig 3: at diagnosis, bone marrow biopsy showed hypocellularity with megakaryocytic hyperplasia and dysplasia.

Bone marrow karyotype and FISH analysis at diagnosis revealed isolated monosomy 7 in approximately 20% of the interphase cells examined.
Fig 4: (at diagnosis) array CGH showed heterozygous deletion encompassing GATA2.

Familial testing for GATA2 mutations revealed no mutations in both parents.
Discussion Points

1. *GATA2*-related spectrum disorders with emphasis on pediatric MDS
2. Molecular detection for germline *GATA2* mutation in pediatric MDS
3. Role of identification of somatic mutations
Role of GATA2 in hematopoiesis

The GATA2 gene encodes a chief hematopoietic transcription factor.

Through its 2 zinc finger domains (ZFs) can occupy GATA DNA motifs in several thousand genes.

GATA2 plays a critical role in hematopoietic development [hemogenic endothelium to hematopoietic stem cells (HSC) transition, and required for HSC survival and self-renewal].

Role of GATA2 in hematopoiesis

Phenotype of GATA2 deficiency

GATA2 germline mutations result in loss of the second ZF (ZF2) and haplo-insufficiency.

Hence the term GATA2 deficiency or haploinsufficiency widely accepted to describe GATA2-spectrum disorders.
Evolution of MDS in GATA2 deficiency background

- **Karyotypes:**
  - monosomy 7, der(1;7)
  - trisomy 8
  - normal

- **Somatic mutations:**
  - $ASXL1$, $SETBP1$, $STAG2$

- **Cellularity & CBC normal, no infections**
- **Cellular deficiencies:**
  - BMF(RCC), B, NK, DC, CD4+, monocytes, macrophages
- **AML, adult MDS, CMML, MPN**

**Timeline**
- Birth
- ~10 years
- ~20 years
Phenotype of GATA2 deficiency

Familial MDS/AML

Pediatric MDS

MonoMac syndrome/DCML deficiency

Pulmonary alveolar proteinosis

Emberger syndrome

CMML/JMML

Aplastic anemia

Chronic neutropenia
GATA2-related Pediatric MDS

EWOG-MDS studies of 426 with primary pediatric MDS and 82 of secondary MDS

Germline GATA2 mutations account for 15% of advanced and 7% of all primary pediatric MDS; versus <1% in adult MDS.

72% of adolescents with MDS and monosomy 7 harbor a germline mutation in GATA2.

~70% of pediatric MDS occur sporadically without family history of hematologic malignancies.

GATA2 mutations were absent in secondary MDS (therapy-related or post aplastic anemia)

**GATA2-related Pediatric MDS**

GATA2 screening should be considered for all pediatric MDS with monosomy 7, trisomy 8, or in patients with non-hematologic features of GATA2 deficiency.

Interestingly, monocytopenia is not a consistent immunological feature in pediatric cohort, but rather B-lymphopenia.

Spectrum of GATA2 Mutations

A

NM_032638.4

B

NONCODING 10.5%

TRUNCATING frameshift > stop gain > splice site 53%

MISSENSE 33%

OTHER 3.5%

C

Exon2 Intron2 Exon3 Exon4 Intron4 Exon5 Exon6 GATA2

Genetic causes of GATA2 deficiency

1. Truncating mutations prior or within ZF2 ~60%
   ZF1: cofactor binding

2. Missense mutations within ZF2 ~30%
   ZF2: DNA & cofactor binding

3. Noncoding mutations in +9.5kb regulatory site ~5-10%

Wlodarski MW et al. Seminars in Hematology May 2017
GATA2 germline mutation testing

Multimodal approach is needed to assess all potential GATA2 mutations

- Mutations occur throughout the gene
- Whole exome sequencing will miss intronic variants and possibly whole gene deletions

Proposed diagnostic work up for suspected GATA2 deficiency

- Sanger- or NGS-base analysis of coding sequence, intron 4 enhancer
- Copy number analysis to rule out GATA2 gene deletion

Recent studies have investigated the potential role for acquired (somatic) mutation testing in GATA2-MDS patients. Somatic mutations may have potential prognostic effect in children with inherited GATA2 mutations.

**ASXL1, NRAS, RUNX1, SETBP1, TP53, WT1, IDH2**

Chiba K et al. *Haematologica*, Oct. 2015

**RUNX1, SETBP1, IKZF1, and CRLF2**


**ASXL1, SETBP1** (unpublished observations)

Wlodarski MW et al. *Seminars in Hematology* May 2017
Treatment & Future Directions

GATA2 mutations are not independently prognostic, but the high risk for cytogenetic evolution, cytopenias, and advanced disease warrant close monitoring.

HSCT is recommended prior to the development of monosomy 7 and/or increasing blasts.

More studies are needed to assess the impact of additional acquired somatic mutations on prognosis and clinical management.

Proposed Diagnosis

Pediatric MDS with a germline GATA2 heterozygous deletion, monosomy 7, and somatic CRLF2 mutation

Panel Diagnosis

Refractory Cytopenia of Childhood (RCC) with germline GATA2 mutation
Thank You.

Baylor College of Medicine

Texas Children’s Hospital
Fig. 2  GATA2 germline mutations in children and adolescents with MDS. Structure of GATA2 protein with two functionally important zinc finger (ZF) domains marked in green (ZF1) and red (ZF2). 42 germline GATA2 mutations are depicted, as previously reported by Wlodarski et al. [6]. Red-color circles represent affected amino acids. Numbers in brackets indicate the numbers of cases with a particular variant. **Bold font** denotes nonsense mutations, whereas **bold italic font** demonstrate splice site mutations.
At disease progression (after 2nd BMT), FISH analysis detected a chimeric pattern of monosomy 7 in approximately 22.4% of interphase cells examined.