Germline *GATA2* Mutation and Bone Marrow Failure

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KEYWORDS

• GATA2 • Monocytopenia • Micromegakaryocytes • MDS

KEY POINTS

- GATA2 deficiency has variable clinical presentations including warts, mycobacterial infections, fungal infections, lymphedema, pulmonary alveolar proteinosis, aplastic anemia, myelodysplastic syndrome, or acute myeloid leukemia.
- Bone marrow histology in symptomatic GATA2 deficiency is hypocellular with characteristic abnormal megakaryocytes, separated nuclear lobes, micromegakaryocytes with hypolobated nuclei, loss of monocytes and hematogones, and an inverted CD4:CD8 ratio.
- Historical features that suggest underlying GATA2 deficiency include persistent warts, lymphedema, pulmonary alveolar proteinosis or disseminated, and/or unusual infections.
- Bone marrow transplantation can reverse the infectious, hematopoietic, and pulmonary complications. Without bone marrow transplantation, there is a significant risk of transformation.

INTRODUCTION

GATA2 encodes a zinc finger transcription factor necessary for normal hematopoiesis located on chromosome 3q21.2. The protein contains 2 zinc fingers and a nuclear localization signal. GATA2 binds to the consensus sequence W/GATA/R (W = A or T and R = A or G) in promoter/enhancer regions of target genes including *SPI1* (PU.1), *LMO2*, *TAL1*, *FLI1*, and *RUNX1* to regulate endothelial to hematopoietic transition in the early embryo, the formation of hematopoietic stem cells (HSCs) and definitive hematopoiesis.[1] In the adult, GATA2 is critical for maintenance of the stem cell

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pool through HSC survival and self-renewal. GATA2 is also important for production of megakaryocytes, mast cells, natural killer (NK) cells and monocytes.[2]

In mice, *Gata2*$^{-/-}$ leads to embryonic lethality at embryonic day 9.5 owing to a lack of definitive hematopoiesis, whereas *Gata2*$^{+/-}$ mice have decreased progenitor cell numbers and reduced transplant repopulation.[3,4] The level of functional GATA2 protein is critical for HSC survival and normal hematopoiesis, as shown by conditional *Gata2* mouse models.[5]

Pathogenic germline variants in *GATA2* affect exons and critical regulatory intronic regions of the gene, as well as deletions. Several groups described constellations of symptoms, each giving them different names: MonoMAC[6,7]; familial myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)[8]; DCML deficiency (dendritic cell, monocyte, B, and NK lymphoid deficiency)[9]; and Emberger syndrome (MDS with lymphedema).[10] In 2011, it was recognized that underlying all of these autosomal-dominant disorders were heterozygous germline mutations in *GATA2*, hence, this syndrome is best referred to as GATA2 deficiency.

Germline pathogenic variants include deletions, missense, nonsense, frameshift, and splice site changes and alterations of intronic regulatory elements. Mechanistically, all variants seem to lead to haploinsufficiency.[11] Most pathogenic variants cluster in the 2 zinc fingers, leading to a nonfunctional protein unable to bind DNA or other transcription factor partners.[12,13] Whole or partial gene deletions produce haploinsufficiency by hemizygosity.[14] Mutations in the intron 5 enhancer lead to reduced transcription of the *cis* allele.[15] Frameshift mutations lead to nonsense mediated decay, premature stop codons, or splice site alterations.[2]

Since gene identification in 2011, the number of cases identified has increased steadily, with associated phenotypic expansion. We briefly review the clinical manifestations with a focus on the bone marrow failure aspects, discuss management, and bone marrow transplantation.

CLINICAL MANIFESTATIONS

Hematologic

Patients molecularly diagnosed with germline *GATA2* mutations at birth, owing to an affected family member, are immunologically and hematologically normal. Over time, the majority evolve cytopenias, including deficiencies in monocytes, B-lymphocytes, dendritic cells, and NK cells. However, there is significant variability in this presentation (**Box 1**). Profound monocytopenia is one of the most consistent features, but only later in the development of disease. Unlike other marrow failure syndromes, anemia and thrombocytopenia are uncommon early presentations, except in those patients who present with aplastic anemia (AA), MDS, or AML. Lymphocyte subset evaluation may identify B and NK cell cytopenias. Pediatric MDS with germline *GATA2* mutation can present without recognized immunodeficiency.[16,17]

Bone marrow is typically hypocellular (**Fig. 1**A) with characteristic features, including atypical megakaryocytes, ranging from large abnormal forms with separated nuclear lobes (osteoclast-like), to smaller forms with separated nuclear lobes, micromegakaryocytes, to small hypolobated or mononuclear megakaryocytes[18] (**Fig. 1**B–E). In some cases, the marrow is very hypocellular with very few megakaryocytes. Immunohistochemistry for CD61 performed on core biopsies may help to identify megakaryocytic atypia (see **Fig. 1**E); immunohistochemistry for CD34 can help to identify increased blasts (**Fig. 1**L). Patients with disseminated nontuberculous mycobacterial infections (NTM) may have granulomata in the marrow with mycobacteria. Review of aspirate smears is critical for assessing progression to MDS, which can be subtle or hindered