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Germline *GATA2* Mutation and Bone Marrow Failure

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SYNOPSIS

GATA2 deficiency is an immunodeficiency and bone marrow failure disorder caused by pathogenic variants in *GATA2* which lead to haploinsufficiency. It is inherited in an autosomal dominant pattern or can be due to *de novo* sporadic germline mutation. Patients commonly have B-, DC-, NK- and mono- cytopenias, and are predisposed to the development of MDS, AML, and CMML. Patients may also suffer from disseminated HPV and mycobacterial infections, pulmonary alveolar proteinosis and lymphedema. Bone marrow from *GATA2* deficient patients eventually takes on a characteristic hypocellular myelodysplasia with loss of monocytes and hematogones, megakaryocytes with separated nuclear lobes, micromegakaryocytes and megakaryocytes with hypolobated nuclei.

Keywords

GATA2; monocytopenia; micromegakaryocytes; MDS

Introduction

GATA2 encodes a zinc finger transcription factor necessary for normal hematopoiesis located on chromosome 3q21.2. The protein contains two 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

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embryo, the formation of hematopoietic stem cells (HSCs) and definitive hematopoiesis¹. In the adult, GATA2 is critical for maintenance of the stem cell pool through HSC survival and self-renewal. GATA2 is also important for production of megakaryocytes, mast cells, NK cells and monocytes².

In mice *Gata2*^{-/-} leads to embryonic lethality at embryonic day 9.5 due to lack of definitive hematopoiesis, while *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 models⁵.

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 MDS/AML (myelodysplastic syndrome/acute myeloid leukemia)⁸; DCML deficiency (dendritic cell, monocyte, B, and natural killer (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 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 appear to lead to haploinsufficiency¹¹. Most pathogenic variants cluster in the two zinc fingers, leading to a non-functional protein unable to bind DNA or other transcription factor partners^{12,13}. Whole or partial gene deletions produce haploinsufficiency by hemizygosity¹⁴. Mutations in the intron 5 enhancer lead to reduced transcription of the *cis* allele¹⁵. Frameshift mutations lead to nonsense mediated decay, premature stop codons or splice site alterations².

Since gene identification in 2011, the number of cases identified has grown steadily, with associated phenotypic expansion. We will 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, due to an affected family member, are immunologically and hematologically normal. Over time the majority will evolve cytopenias, including deficiencies in monocytes, B-lymphocytes, dendritic cells (DCs) and natural killer (NK) cells. However, there is significant variability in this presentation (Table 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 who present with aplastic anemia (AA), MDS or AML. Lymphocyte subset evaluation may identify B and NK cytopenias. Pediatric MDS with germline *GATA2* mutation can present without recognized immunodeficiency^{16,17}.

Bone marrow is typically hypocellular (Fig 1A) 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 megakaryocytes¹⁸ (Fig 1B-E). In some cases, the marrow is very hypocellular with very few megakaryocytes. Immunohistochemistry (IHC) for CD61 performed on core biopsies may help identify megakaryocytic atypia (Fig 1E); IHC for CD34 can help identify increased blasts (Fig 1L). 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 by paucicellular specimens. GATA2 deficiency-associated hypocellular MDS may display multilineage dysplastic changes (Fig 1F-H) involving erythroid precursors (nuclear budding, binucleation, megaloblastic changes), myeloid precursors (nuclear hyposegmentation, hypogranularity, nuclear to cytoplasmic maturation asynchrony) and markedly dysplastic megakaryocytes.

Bone marrow flow cytometry often shows hypogranular granulocytes, absent monocytes and hematogones (B cells progenitors), reduced mature B cells and NK cells and inverted CD4:CD8 ratios with relatively increased CD57+ T-cells (Fig 2). Absent hematogones, inverted CD4:CD8 ratio with mono-, NK and B cell cytopenia differentiate GATA2 deficiency from idiopathic aplastic anemia (AA)¹⁹. In pediatric MDS patients lack of B cells and B cell progenitors predicts GATA2 deficiency¹⁷. Decreased or absent intron RSS-Kde recombination excision circles are also common in pediatric MDS due to GATA2 deficiency¹⁷. Within the bone marrow compartment there is a loss of CD34+, CD38- multi-lymphoid or lymphoid-primed multipotent progenitors and depletion of CD38+ granulocytic monocytic progenitors². Increased serum FLT3 ligand tracks with worsening of bone marrow failure and clinical disease in GATA2 patients²⁰.

Since GATA2 deficiency can present as AA (Fig 1I-J), it is critical to differentiate it from idiopathic AA²¹. One report identified five patients who presented with AA who had *GATA2* regulatory region mutations²². Mild chronic neutropenia with monocytopenia can also be a presentation of GATA2 deficiency, ten such patients were found in French severe congenital neutropenia registry²³.

Hematopoietic Malignancies—GATA2 deficiency predisposes to leukemia: an original description was familial AML^{8,24,25}. Myeloid neoplasms of any type eventually develop in up to 75% of patients²⁶. The average age of onset for myeloid neoplasms varies, depending on the cohort studied, but overall has been shown to be 12–35 years old with a median of 19.7 years²⁷. However, myeloid neoplasms due to this germline predisposition can develop into late adulthood, as late as the eighth decade has been reported and should be recognized²⁶. The development of myeloid neoplasms is remarkably inconsistent within families. The underlying biology of these differences is not understood²⁸.

MDS is very common in GATA2 deficiency, often accompanied by cytogenetic changes, most commonly monosomy 7 (41% of cases), trisomy 8 (15%) and trisomy 1q^{7,19,29}. Interestingly, del5q has not been reported in GATA2 deficiency, nor have ringed sideroblasts. One study found 7% of primary pediatric MDS and 15% of children with advanced MDS to

have *GATA2* deficiency. Of those with pediatric MDS and monosomy 7, 37% had germline *GATA2* mutations; in adolescents with MDS plus monosomy 7, 72% had underlying germline *GATA2* mutations, suggesting that *GATA2* deficiency may be the most common genetic defect predisposing to pediatric MDS¹⁶. Therefore, it is critical for all pediatric MDS and all AML patients with a somatic *GATA2* mutation to be screened for germline mutations^{16,30}.

The mechanisms behind the development of MDS in *GATA2* deficiency are only partially understood. It is hypothesized that the combination of HSC loss, bone marrow stress and clonal evolution drive the development of dysplasia and transformation to leukemia (Fig 3)^{27,31,32}. Bone marrow stress occurs due the progressive cytopenias and recurrent infections³³. Clonal evolution can occur through development of cytogenetic clones and progression to MDS/AML (Fig 1K-N). The most common gene with somatic mutation in hematopoietic clones is *ASXL1*, found in 29% in one series³⁴. Wang et al. identified *ASXL1* mutations in 2/6 patients screened within three families³⁵. Bodor et al. identified a family with a pair of siblings with *GATA2* mutation, one with a concurrent *ASXL1* mutation and MDS and the other without either²⁴. Acquisition of *ASXL1* mutations may cooperate with germline *GATA2* mutations to drive the hypoplastic bone marrow to a pro-leukemic hyperplastic state³⁶.

Other somatic mutations have also been reported. In the families described by Wang et al., two members had *NRAS* mutations, and others had mutations in *RUNX1*, *TP53*, *STAG2* and *SETBP1*³⁵. Ding et al. described a father-son pair, both of whom had *STAG2* mutations, but in different genomic locations³⁷. Fujiwara et al. described a patient who progressed to MDS/AML with somatic mutations in *EZH2*, *HECW1* and *GATA1*³⁸. Loyola and colleagues screened 60 *GATA2* deficiency patients with MDS and found recurrent mutations in *SETBP1*, *ASXL1*, *STAG2*, *RUNX1*, *CBL*, *EZH2*, *NRAS*, *JAK3* and *PTPN1*³⁹. Fisher et al. described two pediatric *GATA2* deficiency MDS patients- one with *RUNX1*, *SETBP1* and *IKZF1* somatic mutations, and the other with a *CRLF2* mutation⁴⁰.

MDS and AML are the best described myeloid neoplasms in *GATA2* deficiency. However, chronic myelo-monocytic leukemia (CMML) in *GATA2* deficiency has been associated with monocytosis and often have *ASXL1* somatic mutations^{27,29,34}.

A single case of pre-B cell acute lymphoblastic leukemia occurred in an adolescent girl who developed disseminated *M kansasii* after chemotherapy⁴¹. She also had other features of *GATA2* deficiency including warts as a young child, megakaryocyte dysplasia, monosomy 7, disseminated fungal disease, PAP, and long standing monocytopenia.

GATA2 plays an important role in germline predisposition to AML, but also in *de novo* AML when *GATA2* is somatically altered. A unique mechanism is involved in the pathogenesis of inv(3) AML, which repositions a *GATA2* binding element upstream of *EVII*, an oncogene, increasing *EVII* expression and decreasing *GATA2* expression, thus creating somatic haploinsufficiency within the leukemic blasts^{42,43}. Epigenetic alterations also lead to decreased *GATA2* expression in normal karyotype AML⁴⁴. *GATA2* levels are

tightly regulated throughout hematopoiesis, and dysregulation of the level of GATA2 promotes stem cell loss, dysfunction and leukemogenesis.

Immunologic

Much of the immune dysregulation in GATA2 deficiency is attributed to cytopenias and the underlying loss of stem cells⁴⁵. However, quantitative cytopenia does not fully explain the breadth of immune dysregulation seen. Low numbers and dysfunction of NK cells is a key feature of GATA2 deficiency. GATA2 is required for normal and complete maturation of NK cells, maintenance of the CD56^{bright} population, and full cytotoxicity⁴⁶. Schlums and Jung found that GATA2 deficiency leads to loss of NK cell progenitors, thus decreasing canonical NK cell differentiation⁴⁷. Adaptive NK cells may persist in GATA2 deficient patients, even after these patients have lost their canonical NK cells. The remaining NK cells have decreased CXCL12/CXCR4-dependent chemotaxis, while the B cells have increased CXCL12-induced chemotaxis⁴⁸. Ruiz-Garcia studied four patients and showed that those with worse clinical phenotype had increased T cell senescence⁴⁹.

GATA2 deficient patients also get panniculitis, erythema nodosum and arthritis. Autoimmune hepatitis in GATA2 deficiency has been reported⁵⁰. It is important to keep the infection predisposition in mind, as erythema nodosum is more common in patients with active mycobacterial disease. There may also be a T regulatory cell, DC and increased CD38-CD21- B cell deficiency². These autoimmune complaints may present initially to rheumatologists⁵¹. Hypogammaglobulinemia clinically consistent with common variable immunodeficiency also occurs⁵².

Infectious

NTM infections were found in up to 53% of patients in one study²⁹, often disseminated and difficult to control, due to slow (*Mycobacterium avium* complex (MAC), *M kansasii*, and *M szulgai*) and rapid growing (*M fortuitum*, *M abscessus*, and *M chelonae*) organisms^{29,53,54}. *M kansasii* can cause a characteristic necrotizing mediastinal lymphadenitis⁵⁵. Disseminated NTM disease correlates with cytopenias in adolescents or young adults; it is uncommon in childhood when the cell numbers are intact. Smoking may increase the risk for dissemination of NTM in the setting of already compromised alveolar macrophage function⁵⁵.

Other severe bacterial infections include *Clostridium difficile* and group C streptococcal infections²⁹. One case of *P jiroveci* pneumonia was reported⁵⁶. Approximately 16% of patients had fungal infections including aspergillosis, disseminated histoplasmosis, and candidiasis²⁹.

Human papilloma virus infections occur in two thirds as recalcitrant warts, condylomata, and/or cervical dysplasia. Persistent warts in a patient with cytopenias or bone marrow failure suggests GATA2 deficiency.

Epstein Barr virus (EBV) viremia was found in 11% of patients in one study²⁹, including a variety of EBV-associated pathologies such as mononucleosis, chronic active EBV, hydroa vacciniforme-like lymphoma with hemophagocytic lymphohistiocytosis and smooth muscle

cell tumors⁵⁷. EBV associated spindle cell tumor and demyelinating sensorimotor polyradiculoneuropathy have been reported^{58,59}. Severe disseminated herpes simplex infections are also important to watch for as they can lead to dire complications^{60,61}. Overall, approximately 80% of patients will have infectious complications of their disease leading to significant morbidity and mortality.

Dermatologic

Warts are seen on extremities and genitalia (common or flat type) in about 50% of patients and are difficult to treat.^{62,63} Neutrophilic pustulosis (Sweet syndrome) can be seen in patients who go on to develop MDS or AML. Panniculitis, erythema nodosum and cellulitis have also been described⁶⁴.

Vascular

Kazenwadel et al. showed that *GATA2* is expressed in lymphatic vessels and is a critical regulator of development of lymphatic vessel valves⁶⁵. Patients with gene deletions and stop codons appear to be at especially increased risk of lymphedema. Lymphedema, particularly in an adolescent or young adult with cytopenias, suggests *GATA2* deficiency. *GATA2* is also expressed in the vascular epithelium and platelets, and thrombosis occurs in a significant number of patients. The risk for thrombosis is likely multifactorial, since *GATA2* deficient patients often have other risk factors, including infection and malignancy. Maternal-related preterm labor has been observed, as well as frequent miscarriage.

Pulmonary

Pulmonary alveolar proteinosis (PAP) is a common and life-threatening complication of *GATA2* deficiency caused by over-accumulation of surfactant in alveoli impairing gas exchange. It is typically suspected on CT scan and confirmed on PAS staining or electron microscopy of bronchoalveolar lavage specimens⁶⁶. PAP in *GATA2* deficiency is likely due to alveolar macrophage dysfunction, in part due to abnormal GM-CSF-related signaling. Griese et al. identified two *GATA2* deficiency patients in a cohort of GM-SCF autoantibody negative PAP patients⁶⁷. Svobodova et al. identified a *GATA2* deficient patient who presented with persistent diffuse parenchymal lung disease in childhood⁶⁸. Pulmonary hypertension has been seen in *GATA2* deficiency, both preceding and following the development of severe PAP^{69,70}. Subpleural and paraseptal emphysematous changes in the lung may be seen long before overt clinical manifestations.

Eye and Ear

Congenital deafness has been observed in *GATA2* deficiency, probably more often in those with gene deletions or stop codon mutations. Using conditional mouse models, Haugas et al. showed that *GATA2* is required for proliferation of the epithelium in the semicircular duct and for clearance of mesenchymal cells to generate the vestibular perilymphatic space⁷¹. Berry and colleagues reported a case of central retinal vein occlusion in *GATA2* deficiency, which may have represented underlying hypercoagulability due to cellular or vascular defects⁷².

Oncologic

Solid Tumors—A variety of solid malignancies have been reported, most related to HPV infection, such as genital dysplasias and invasive squamous cell carcinomas (SCC). HPV associated head and neck SCC have also been seen^{20,29}. EBV-related tumors, such as leiomyosarcomas occur. Crall et al. reported a case of Merkel cell carcinoma in an adult with both GATA2 deficiency and neurofibromatosis type 1⁷³. Lastly, in the NIH cohort there is significant frequency of breast cancer in (approximately 20% in women above 35 years old), for unclear reasons²⁹.

Hematopoietic stem/progenitor Cell Transplant

Hematopoietic stem/progenitor cell transplant (HSCT) is highly effective in the treatment of GATA2 deficiency. HSCT restores normal hematopoiesis, resolves MDS, clears long standing underlying infections, and resolves PAP and pulmonary hypertension in patients with GATA2 deficiency⁷⁴. The optimal timing of transplant is unclear. Our institutional strategy has been to proceed with transplant when cytopenias are present, if life threatening infections have occurred, or if PAP or other significant organ dysfunction develops. However, the disease course is often difficult to predict and patients may be diagnosed only in the later stages of the disease.

The best choices for preparative regimen, donor source and graft versus host disease (GVHD) prophylaxis are areas of current investigation. Cuellar-Rodriguez and colleagues reported successful transplantation for GATA2 deficiency in six patients⁷⁴. Since that time multiple other groups have reported good outcomes with HSCT for GATA2 deficiency. Both myeloablative and reduced intensity preparative regimens have been successful. Matched related and unrelated peripheral blood stem cells (PBMCs), matched and haploidentical bone marrows, and umbilical cord grafts have all been reported.

Ciucilli et al. reported a young patient who received a transplant from his matched brother using an ablative regimen⁷⁵. Ramazan et al. reported a very young patient with Emberger syndrome and MDS who underwent successful myeloablative HSCT with resolution of MDS⁷⁶. Lubking et al. described an adult with MDS and *ASXL1* somatic mutation who underwent successful HSCT from an unrelated PBMC donor with resolution of MDS and condylomata⁷⁷. Maeurer et al. described a young adult with severe disseminated HPV skin disease treated with matched related HSCT⁷⁸. Post HSCT her condylomata disappeared and her cervical cancer *in situ* resolved. These authors suggested pre-harvest donor HPV vaccination if not previously vaccinated. Malhi and colleagues reported two pediatric cases of HSCT using cord blood: the first patient had AML with MDS-related changes and received a myeloablative regimen; the other had MDS and received reduced intensity conditioning⁷⁹. Saida et al. reported a pediatric patient with successful reduced intensity HSCT⁸⁰.

Following up Cuellar-Rodriguez et al, Grossman et al. reported eight more patients (total 14), from an open HSCT trial specifically for GATA2 deficiency⁸¹. This group included both matched and haploidentical donors. The authors currently use a myeloablative regimen to

improve engraftment and reduce the risk of relapse, beyond what was seen in the prior cohort.

GVHD has been seen in GATA2 HSCT at typical or increased rates, but different prophylaxis regimens make it difficult to generalize rates. Shah et al. reported a pair of monozygotic twins who both underwent HSCT for GATA2 deficiency from the same donor with the same conditioning regimen one twin developed severe acute GVHD of the skin and gastrointestinal tract requiring immunosuppression for 1.5 years, the other twin only had grade 1 GVHD of skin not requiring systemic corticosteroids⁸². This unique report highlights the nonheritable factors affecting GVHD outcomes. It is hypothesized that prior and peri-transplant exposures, especially infectious, may contribute to such differences.

Patient Monitoring and Screening

Currently, there are no guidelines for patient care and monitoring. However, expert opinion in the literature and our practice are given in Box 1. Once a *GATA2* mutation has been identified and cytopenias of any degree are noted we start daily azithromycin prophylaxis for NTM. HPV vaccination should be given on the full schedule, as well as other childhood vaccines. We have not seen problems with live virus vaccines in children with normal counts or marrows. BCG vaccination has also not been a problem in GATA2 deficiency as long as counts are normal. Baseline bone marrow aspiration, biopsy and cytogenetics should be performed. We follow at least bi-annual CBC with differential, and yearly lymphocyte subset evaluation, bone marrow biopsy and aspiration, pulmonary function testing, comprehensive skin examinations and for females, gynecologic examinations. Good oral hygiene and regular dental visits are recommended, especially surveillance for HPV-related oral disease. If MDS develops, prompt referral to an HSCT team with disease specific knowledge is advisable. Likewise, if a GATA2 deficiency patient develops aplastic anemia, prompt HSCT is advisable as immunosuppressive therapy appears to increase risk and delays definitive treatment.

Overall, HSCT is the only curative option for GATA2 deficiency patients; gene therapy is unlikely to be available any time soon. Screening of potential donor family members for *GATA2* mutation, in addition to HLA typing, is absolutely essential, given the wide variation in GATA2 deficiency phenotype and age at presentation. While the timing of transplantation is hard to precisely prescribe, the consequences of waiting until after major infections, organ dysfunction or malignancy develop are dire and baleful.

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Box 1: Screening Recommendations

Twice yearly CBC with differential

Yearly Lymphocyte Subset Evaluation- monitor monocyte loss or outgrowth

Yearly bone marrow biopsy and aspiration with mycobacterial culture, flow cytometry and cytogenetics; consider somatic mutation panel testing

Yearly Pulmonary Function Testing

Yearly Comprehensive Skin Examination

Yearly Gynecological Exam

Recommendations for testing and frequency listed here are only based on expert opinion and not evidence based at this time.

KEY POINTS

- GATA2 deficiency has variable clinical presentations including warts, mycobacterial infections, fungal infections, lymphedema, pulmonary alveolar proteinosis, aplastic anemia, MDS or AML.
- Bone marrow histology in symptomatic GATA2 deficiency is typically hypocellular and has characteristic abnormal megakaryocytes with separated nuclear lobes; micromegakaryocytes with hypolobated nuclei; loss of monocytes and hematogones; and an inverted CD4:CD8 ratio. Overt morphologic evidence of dysplasia is variable.
- Historical features of bone marrow failure or MDS that suggest underlying GATA2 deficiency include persistent warts, lymphedema, pulmonary alveolar proteinosis or disseminated and/or unusual infections. However, in childhood MDS and leukemia can be initial presentations.
- Bone marrow transplantation can reverse the infectious, hematopoietic and pulmonary complications seen in GATA2 deficiency. Without bone marrow transplantation, there is a significant risk of transformation to MDS/AML or CMML.

Figure 1. The range of bone marrow pathologies seen in GATA2 deficiency. (A-C) Bone marrow and immunodeficiency disorder with germline *GATA2* mutation.

(A) Hypocellular marrow for age (late adolescent patient with history of warts and infections) with characteristic atypical megakaryocytes with separated nuclear lobes present on (B) core biopsy and (C) aspirate. No overt morphologic dysplastic changes are present in myeloid and erythroid precursors. Cytogenetic analysis showed a normal karyotype. CBC with differential and peripheral blood flow cytometric analysis revealed severe monocytopenia, B/NK-cell lymphopenia. **(D-H) Myelodysplastic syndrome with multilineage dysplasia and germline *GATA2* mutation.** The bone marrow is hypocellular for age (young adult in 3rd decade) with (D) increased atypical megakaryocytes with separated nuclear lobes, hypolobated and mononuclear forms. (E) Megakaryocytes are

highlighted by immunohistochemistry stain for CD61 (E, inset small positive cell in center) revealing micromegakaryocytes. Aspirate smear shows (F) dyserythropoiesis with nuclear budding and (H) binucleation; myeloid maturation asynchrony with (G) nuclear hyposegmentation and (H) hypogranular myeloid cells. Cytogenetic analysis showed monosomy 7. CBC with differential and peripheral blood flow cytometric analysis revealed moderate pancytopenia with severe monocytopenia, and B/NK-cell lymphopenia. **(I-J) Aplastic anemia, with unrecognized germline *GATA2* mutation at diagnosis.** Bone marrow is markedly hypocellular with trilineage hypoplasia. Aspirate is paucicellular with insufficient cells to evaluate for dysplastic changes. Cytogenetic analysis failed due to poor mitotic index. Bone marrow flow cytometry analysis was not performed. The patient later evolved to MDS and a *GATA2* mutation was identified. **(K-M) Acute myeloid leukemia with myelodysplasia related changes and germline *GATA2* mutation.** (K) Hypocellular marrow from a man (early 3rd decade) previously diagnosed with aplastic anemia that had evolved to MDS with monosomy 7. Marrow shows background hemosiderin laden macrophages from red cell transfusions. (L) Immunohistochemistry stain for CD34 reveals (M) numerous CD34 positive blasts which are also positive for CD117. (N) Aspirate smear showed increased blasts (35% on differential count) indicative of progression to acute myeloid leukemia. Cytogenetic analysis showed monosomy 7.

Figure 2. Flow cytometry analysis of bone marrow in idiopathic aplastic anemia (AA) and GATA2 deficiency.

(A) Monocytic cells, designated by positivity for CD14 and HLA-DR (within red box) are typically present in the bone marrow of AA and disproportionately decreased to absent in GATA2 deficiency; all nucleated cells in the marrow are gated. (B) Mature B-cells, marked by positivity for CD19 and CD20 (within red box), are typically present in AA and reduced to absent in GATA2 deficiency; lymphocytes in the marrow are gated. (C) Bcell precursors (hematogones; within red box) are often reduced but detectable in AA, but in GATA2

deficiency there is an absence of B-cell precursors. CD19+ cells in the bone marrow are gated; the cells outside of the red box are mature B-cells which are CD20+ and CD10-. (**D**) NK cells, positive for CD56 and negative for CD3, are present in AA and are often absent in GATA2 deficiency; the BM lymphocyte gate is displayed.

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Figure 3. Bone marrow failure and other manifestations of GATA2 deficiency.

GATA2 deficiency syndrome is caused by gene mutations in both the exonic and intronic regulatory regions of the gene leading to haploinsufficiency. Loss of GATA2 protein leads to hematopoietic stem and progenitor (HSPC) cell loss and dysfunction. This depletion leads to a combination of cytopenias- B, DC, NK and monocytes. The resultant immunodeficiency drives infections such as HPV and NTM, and pulmonary alveolar proteinosis. Overall, these factors lead to bone marrow stress, hypocellularity and the ultimate development of bone marrow failure, MDS and AML.

Table 1.**Diagnostic Clue**

Medical History/Physical Exam	PeriDherai Biood
HPV- persistent warts	Monocytopenia
NTM- disseminated	Dendritic Cell cytopenia
Aspergillosis	NK Cell cytopenia
Lymphedema	B Cell cytopenia
Hearing Loss	Neutropenia
Panniculitis	
Erythema nodosum	<u>Bone Marrow Morphology</u>
Thrombosis	Loss of hematogones
Miscarriage/Preterm labor	Micromegakaryocytes
EBV Viremia	Megakaryocytes with separated nuclear lobes
	Inverted CD4:CD8 ratio
	<u>Radiological</u>
	Crazy paving on chest CT
	Subpleural Blebs
	Paraseptal Emphysema
	Ground Glass Opacities
	Splenomegaly