SHORT REPORT

Spectrum of myeloid neoplasms and immune deficiency associated with germline *GATA2* mutations

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Abstract

Guanine-adenine-thymine-adenine 2 (*GATA2*) mutated disorders include the recently described MonoMAC syndrome (Monocytopenia and *Mycobacterium avium* complex infections), DCML (dendritic cell, monocyte, and lymphocyte deficiency), familial MDS/AML (myelodysplastic syndrome/acute myeloid leukemia) (myeloid neoplasms), congenital neutropenia, congenital lymphedema (Emberger's syndrome), sensorineural deafness, viral warts, and a spectrum of aggressive infections seen across all age groups. While considerable efforts have been made to identify the mutations that characterize this disorder, pathogenesis remains a work in progress with less than 100 patients described in current literature. Varying clinical presentations offer diagnostic challenges. Allogeneic stem cell transplant remains the treatment of choice. Morbidity, mortality, and social costs due to the familial nature of the disease are considerable. We describe our experience with the disorder in three affected families and a comprehensive review of current literature.

Introduction

The guanine-adenine-thymine-adenine (*GATA*) family is comprised of six zinc-finger transcription factors that recognize approximately 7 million *GATA* motifs in the human genome [1, 2]. *GATA1* is instrumental in development of erythrocytes, mast cells, eosinophils, and megakaryocytes [3–8] and is implicated in Down syndrome-related acute megakaryocytic leukemia and transient myeloproliferative disorder [9, 10]. *GATA1* is also associated with X-linked thrombocytopenia and dyserythropoeitic anemia (Diamond–Blackfan anemia) [75–77]. *GATA2*, located on 3q21 [11] is pivotal in proliferation of hematopoietic stem cells (HSC) and mutations were first described in aplastic anemia [12–15]. Pedigree studies have initially recognized two mutations in *GATA2* in familial AML, p.T354M, and

p.T355del, both in the second zinc finger (ZF-2) of *GATA2* [16–18], while two other mutations; p.R308P and p.A350-N351ins8 are associated with de novo AML [78]. During erythropoiesis; GATA switching results in displacement of GATA2 by GATA1 from chromatin causing inhibition of GATA2, promoting downstream erythroid differentiation [5, 19]. In contrast, *GATA2* overexpression induces megakaryocytic differentiation in cell lines [20]. *GATA2* exerts an inhibiting influence on the *PU.1* gene which is essential for monocytic, granulocytic, and lymphoid differentiation [21]. In contrast to *RUNX1*, which is essential for generation of HSC, *GATA2* appears to be essential for HSC generation and subsequent survival [22]. Other *GATA* genes perform a diverse array of functions. *GATA3* promotes T-cell lymphopoiesis [23–28] but deficiency has been associated only with hypoparathyroidism, deafness, and renal

disease. *GATA4* has recently been implicated in childhood onset diabetes [29]. *GATA 5* CpG island hypermethylation in renal carcinoma appear to identify aggressive phenotypes with poor outcomes [30]. In animal models, *GATA6* has been shown to orchestrate cardiac muscle hypertrophy in response to pressure stress and increase hepcidin expression in inflammatory states [31, 32]. In summary, GATA factors 1–3 appear to be involved in hematopoiesis, while GATA 4–6 appear to be more important for cardiac development and function [33] although expression has been demonstrated in other endodermal and mesodermal organs such as lung, liver and gonads and gut [34].

The study of germline mutations such as *GATA2* provides profound insights into leukemogenesis, immune dysfunction and cross-talk of seemingly diverse genetic pathways such as *CEBPA, PU.1* [35–38], and *RUNX1* [39–43]. The clinical phenotype of germline *GATA2* mutations include, but is not limited to, spectrum of immune deficits such as MonoMAC syndrome [44–46], dendritic cell, monocyte and lymphoid deficiency (DCML) [47], familial MDS (myelodysplastic syndrome)/AML (acute myeloid leukemia), and Emberger's syndrome [48]. Of note, sporadic mutations in *GATA2* are described and may have no familial implications as described below. Our focus in this article is the haploinsufficiency induced by spontaneous germline mutations in *GATA2* resulting in an autosomal dominant inheritance of diverse phenotypes [44, 46, 49]. The differential diagnosis of *GATA-2* deficiency includes other related disorders with overlapping features and are summarized in Table 1.

Case Series

Family 1

The proband is a 38-year-old Caucasian male, who presented with progressive dyspnea and fatigue of 3 months duration and was found to have pancytopenia. A bone marrow biopsy revealed hypocellular marrow but demonstrated acute myeloid leukemia (AML) with the following cytogenetic abnormalities: t (1; 21) (q10; q10) [9]/+8[4]/46XY [7]. He received standard induction chemotherapy with idarubicin and cytarabine, and his course was complicated by an orbital fungal infection with *Absidia lithemia*, medically and surgically managed, following which he underwent a reduced-intensity conditioning-matched unrelated donor allogeneic hematopoietic stem cell transplant (MUD-Allo-HCT). Posttransplant course was complicated by severe refractory immune-mediated thrombocytopenia requiring a splenectomy and an orbital relapse of AML. Due to history of multiple family members being affected (Fig. 2) by AML and extra genital warts (sister, son, and daughter), congenital lymphedema (son), and cytopenias (sister) a work-up for familial bone marrow failure syndromes was carried out. *GATA2* mutation analysis performed at the National Institutes of Health (NIH) confirmed the presence of a missense mutation (1339A>C, p S447R) in the patient, a female sibling, a son, and a daughter. The female sibling with MDS and viral warts also underwent MUD-Allo-HSCT (hematopoietic stem cell transplant) and remains symptom-free 14 months posttransplant. The probands son and daughter also underwent MUD allogeneic HSCT and are doing very well more than 12 months posttransplant. Patient characteristics and outcomes are shown in Table 2.

Family 2

Family 2 was discovered by the birth of a newborn with dysmorphic features (head size larger than stomach) resulting in a cytogenetic examination in infancy with identification of deletion 3q13.2-q21.3, which includes the *GATA2* gene. The child exhibited monocytopenia without lymphopenia or neutropenia. Dendritic cell activity was not assessed for. The parents were tested and did not have the same gene defect. She is being followed with monthly blood

Table 1. Mutations/disorders in differential diagnosis of *GATA2* deficiency.

Familial MDS/AML [67]	Warts/HPV infections [51]	Mycobacterial infections [68–70]	Congenital lymphedema [71–73, 75, 76]	Pulmonary alveolar proteinosis [77]
TERT/TERC	DOCK 8	*IFNGR1*	*FLT4*	Anti-GM-CSF Ab
CEBPA	CXCR4	*IFNGR2*	*GJC2*	*CSF2RB*
RUNX1	HIV/CD4↓	*IL12RB1*	*FOXC2*	
	TMC6/8	*STAT1* (loss of function; AR and AD)	*SOX18*	
	SPINK5/LEKT1		*CCBE1*	
	STK4/MST1	*IRF8*	*PTPN14*	
		CYBB (macrophage-specific mutation)		
		TYK2		
		ISG15		
		IKKG (NEMO)		

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; HPV, human papillomavirus.

Table 2. Clinical characteristics and outcomes of patients with GATA2 mutations that underwent allogeneic stem cell transplantation.

No.	Diagnosis Age/Sex	Cytogenetics/GATA2 mutation	Associated features	Prior Rx	HCT-CI	CMV	Regimen	ABO/HLA	GVHD Prop	aGVHD Status	Complications	Day 30 Chimerism /Marrow	Day 100 Chimerism /Marrow	Last follow up (Days)
1	AML 38/M	46,XY, t(1;21) [9] + 8[4]46,XY [7] S447R	NK/B-cell def Viral warts Hydrocele	Idarubicin Cytarabine	0	D+ R+	Fludarabine TBI (200)	ABO–mismatch HLA 9/10	Tacrolimus MTX	GI Grade 1	E.Faecalis CMV Anti-platelet antibodies/ Thrombocytopenia	100% Donor 30% Hypo-Cellular	100% Donor 30% Hypo-Cellular	356 (extra medullary relapse day 307)
2	MDS 35/F	S447R	NK/B-cell def Viral warts Infertility	None	0	D– R+	Busulfan Cytoxan	ABO– match HLA 10/10	Tacrolimus MTX	Skin Grade 1	CMV	100% Donor 30% Hypocellular	100% Donor 60% Hypocellular	208
3	MDS 10/F	S447R	NK/B-cell def Viral warts	None	0	D– R+	Cytoxan, TBI Alemtuzumab	ABO– match HLA 9/10	Tacrolimus MTX	Skin Grade 1	C.difficile	100% Donor 30% Hypo-Cellular	100% Donor 20% Hypo-Cellular	247
4	Chronic Neutropenia 7/M	S447R	NK/B cell def Viral warts Emberger's syndrome Pulmonary stenosis	None	0	D– R+	Cytoxan, TBI Alemtuzumab	ABO– match HLA 10/10	Tacrolimus	–	–	Pending 30% Hypo cellular	NA	31

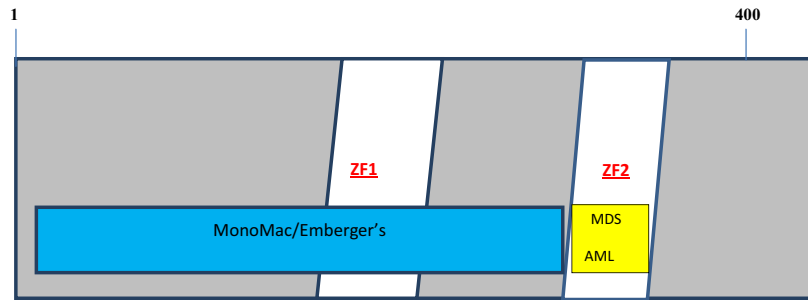MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

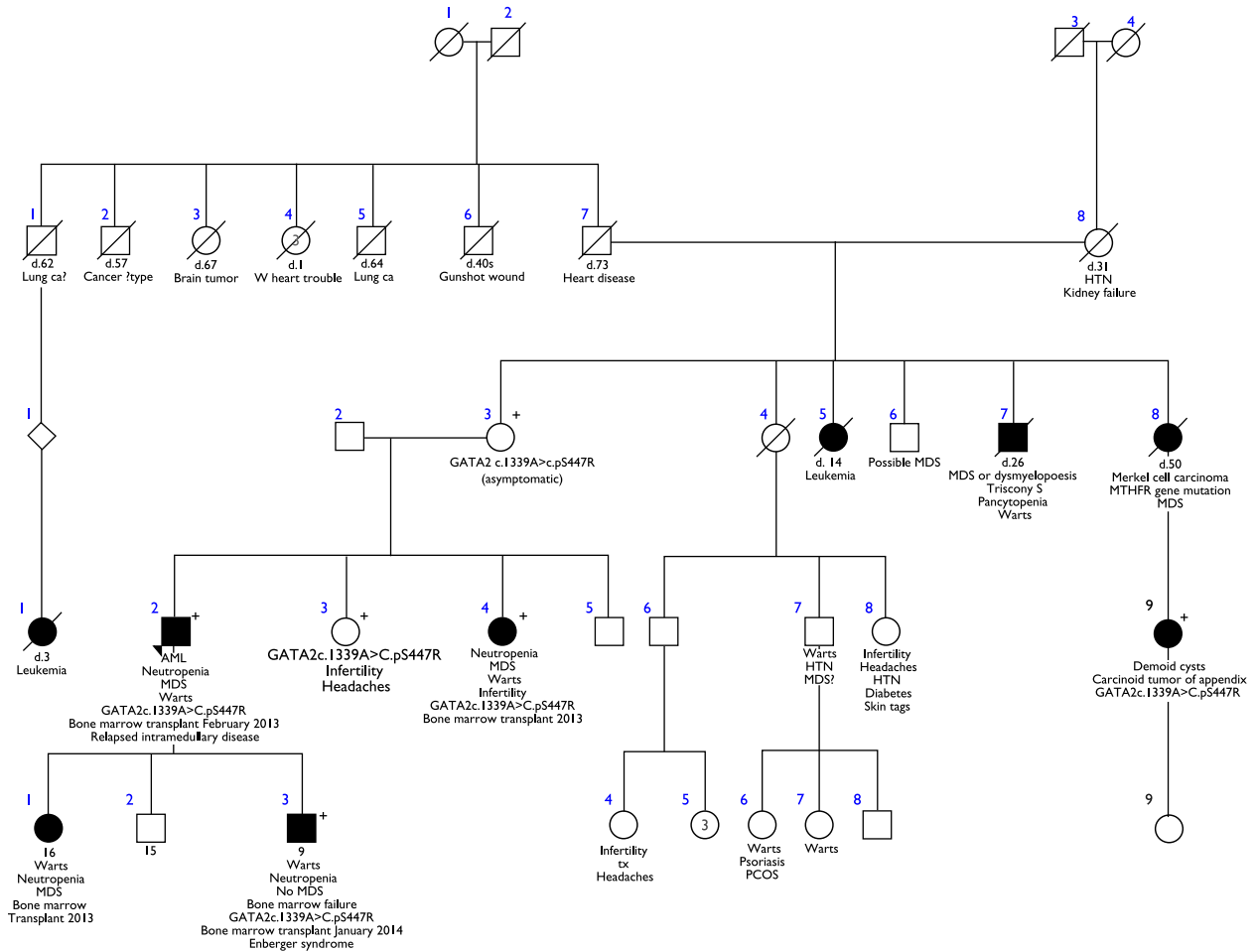**Figure 1.** Genotype/phenotype relations of GATA2 mutations.

Figure 2. Family Tree of Proband 1 with the GATA2 c.1339A>C.pS447R mutation.

tests and has not demonstrated any systemic infections or signs of MDS/AML although cognitive development appears to be delayed.

Family 3

In Family 3, the proband is a Caucasian female who presented at age 17 years with abdominal pain, hemoptysis, and mild pancytopenia. A CT scan revealed mild diffuse thoracic and abdominal lymphadenopathy. A detailed evaluation found acute Epstein–Barr virus (EBV) infection. A bone marrow biopsy was mildly hypocellular with mild erythroid hypoplasia and megakaryocytic hyperplasia with atypia. The cytogenetics were 46, XX [20]. She had a history of recurrent episodes of hidradenitis suppurativa, skin abscesses, folliculitis, otitis media, and throat infections.
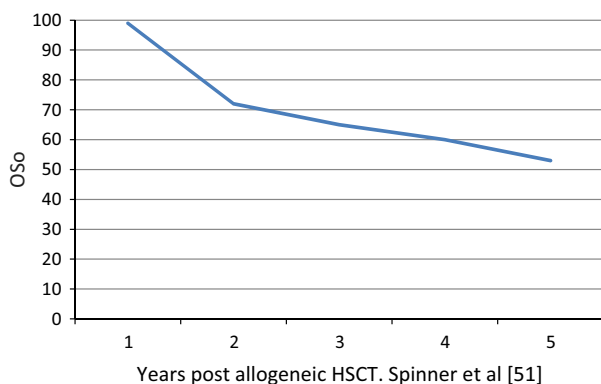
Figure 3. Years post allogeneic HSCT for GATA2 mutation Spinner et al. [53]HSCT, 5 hematopoietic stem cell transplant.

Several years later, she was initiated on therapy with pegylated G-CSF. In spite of this, otitis media and abscesses continued. Two years later, she presented with a hypercatabolic state, with progressive hepato-splenomegaly and constitutional features. A bone marrow biopsy demonstrated progressive megakaryocytic atypia. While cytogenetics were once again normal, however, a MDS-fluorescence in situ hybridization (FISH) panel identified a deletion of -3q21 in 99% of analyzed nuclei. A phytohemagglutinin-stimulated karyotyping of peripheral blood lymphocytes also demonstrated the -3q21 (RPN1 deletion) in 99% of analyzed nuclei. *GATA2* is located within this region, Expression studies confirmed *GATA2* haploinsufficiency. She is awaiting a donor for a MUD-HSCT.

Discussion

MonoMAC syndrome and DCML deficiency

The terms MonoMAC and DCML are synonymous, in terms of the genetic etiology, and refer to a primary immunodeficiency with predisposition to MDS/AML. MonoMAC refers to a recently described syndrome of *MONO*cytopenia and *M*ycobacterium *A*vium *C*omplex infections characterized by germline *GATA2* mutations [44, 46]. DCML, also caused by germline *GATA2* mutations refers specifically to the cytopenias frequently seen in most patients—DCML deficiency (both B and NK cell) [50]. Two independent groups studied 24 individuals with these syndromes and reported similar mutations noted above in familial syndromes (T354M and T355 del). The scope of immune deficiency in this group is vast and not limited to mycobacterial infections. Opportunistic viral (disseminated human papillomavirus [HPV] and HPV-associated squamous cell carcinoma) [51], parasitic and fungal infections, as well as pulmonary alveolar proteino-

sis (*GATA2* is known to influence the phagocytic activity of pulmonary alveolar macrophages) can be seen [52]. A majority of patients with *GATA2* mutations eventually show deficiency of B lymphocytes, NK cells, CD4 lymphocytes, and monocytes [53].

Emberger's syndrome

Emberger's Syndrome is primary lymphedema with cutaneous warts, deafness, and a propensity to develop MDS/AML. Intact *GATA2* function is required for proper lymphatic vascular development during embryogenesis in mice [54]. Ostergaard and colleagues identified eight mutations in *GATA2* in three patients with this syndrome by whole-exome sequencing identifying this mutation as the only common denominator between the group [48]. At least 1 other patient with propensity to varicella zoster and salmonella infections has been reported [48]. Complications secondary to prolonged lymphedema such as secondary cellulitis and deep vein thrombosis (DVT) are frequent [53]. Null mutations in *GATA2* appear to be associated with severe viral infections and lymphedema [52].

Familial MDS/AML

GATA2 overexpression has been documented in one-third to one half of nonfamilial AML and correlates with a poor prognosis with shorter overall and event-free survival when treated with standard chemotherapy [55, 56]. Of the original four families with *GATA2* mutations, described by Hahn et al. with MDS/AML, three had the T354M mutation, and one had deletion T355. Both mutations occurred in the second zinc finger (ZF) of GATA2 (Fig 1). In the T354 mutation families, all members had the mutation but not all had developed hematological disease at least by the time of reporting [16]. Bone marrow biopsies are typically hypocellular in contrast to the common MDS marrow picture, with abundant atypical megakaryocytes in >90% patients [53]. Some patients have also fulfilled the diagnostic criteria for CMML (chronic myelomonocytic leukemia) and LGL (large granular lymphocytic leukemia) suggesting overlap syndromes [53]. Other acquired mutations such as *ASXL1* may herald the development of AML [57]. Increased levels of *FLT3* ligand have also been reported to be associated with clinical progression [58].

Chronic myeloid leukemia

A novel *GATA2* mutation *L359V* has been found in nearly 10% of patients with accelerated or blast phase CML, but not CLL or ALL [59, 60]. This is thought to be mediated through *PU.1* inhibition. It is interesting to note that

GATA2 overexpression or the *L359V gain-of-function* mutation have been associated with AML and CML, respectively; whereas *loss-of-function* mutation of GATA2 such as *T354M* have been linked to MDS. L359 and T354 located in the same region on the second zinc finger of GATA2 thus highlighting the vital role GATA2 plays in hemostasis of myeloid precursors.

Aplastic anemia

Expression of GATA-2 mRNA in purified CD34-positive cells was significantly decreased in aplastic anemia compared with normal subjects when examined by immunocytochemical analysis [61]. The changes extend further to stromal cells, with lower expression of GATA2 in patients with aplastic anemia when compared to controls by RT-PCR-ELISA [62]. *GATA-2* is instrumental in both hematopoiesis and adipogenesis. Overexpression of peroxisome proliferator-activated receptor-gamma (PPAR-γ, an adipogenic factor) and underexpression of GATA2 by mesenchymal stem cells may explain fatty marrow replacement in AA patients [63].

Pediatric neutropenia

A high frequency of *GATA2* mutations has been reported in pediatric patients with mild chronic neutropenia [64]. Analysis of French Neutropenia registry data revealed chronic familial neutropenia in seven families predisposing to MDS/AML associated with *GATA2* mutations that included a complete deletion of *GATA2* locus as well as additional mutations (p.R396Q, R204X, R330X, E224X, A372T, and M388V) [64].

Pulmonary disease

Ventilation-diffusion defects can be demonstrated in about two-thirds of *GATA2*-deficient patients while pulmonary hypertension (PAH) and pulmonary alveolar proteinosis (PAP) are some of the rare manifestations occurring in <20% in one series [53]. PAP in GATA2 deficiency is not due to GM-CSF-(Granulocyte Monocyte- Colony Stimulating Factor) autoantibodies and is refractory to GM-CSF inhalational and subcutaneous therapy [53].

Treatment

Immune deficiency

Allogeneic HSCT remains the main therapy for *GATA2*-deficient patients with immunodeficiency. Timing of HSCT for immune deficiency alone is less well defined as compared to MDS/AML and should focus on risk-benefit ratios for the individual and the family. The incidence of

Table 3. Suggested screening categories for *GATA2* mutation.

Pediatric neutropenia
Monocytopenia
B-cell or NK cell cytopenia
Dendritic cell deficiency
MDS with hypocellular bone marrow
Familial MDS/AML
PAP in absence of anti-GM-CSF autoantibodies
Recurrent extra genital HPV warts or severe refractory genital HPV
Severe viral infection (HSV, EBV)
Lymphedema, often later onset
Sensorineural deafness with immunodeficiency
Disseminated nontuberculous mycobacteria (NTM)
Disseminated or severe fungal infections
Pulmonary NTM without bronchiectasis

Modified from Spinner et al. [53]. MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; HPV, human papillomavirus; PAP, pulmonary alveolar proteinosis; EBV, Epstein–Barr virus.

Table 4. Mutations of *GATA2* resulting in variable phenotypes (Fig. 3) [78].

Mutation type	AA location	Phenotype
Nonsense	337(ZF1)	Emberger syndrome
Missense	254	MonoMAC/DCML
	354(ZF2)	Familial MDS/AML, MonoMAC/DCML
	361(ZF2)	MonoMAC/DCML
	371(ZF2)	MonoMAC/DCML
	373(ZF2)	Emberger syndrome
	396(ZF2)	MonoMAC/DCML
	398(ZF2)	MonoMAC/DCML
Frameshift	1	MonoMAC/DCML
	78	Emberger syndrome
	81	MonoMAC/DCML
	105	Emberger syndrome
	194	Emberger syndrome
	200	MonoMAC/DCML
	259	MonoMAC/DCML
	317(ZF1)	MonoMAC/DCML
	341(ZF1)	Emberger syndrome
In-frame insertion or deletion	355(ZF2)	Familial MDS/AML
	361(ZF2)	MonoMAC/DCML, Emberger syndrome
Large deletion	340–381(ZF1 & 2)	MonoMAC/DCML

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; DCML, dendritic cell, monocyte, and lymphocyte.

HPV, mycobacterial, and fungal infections decreases considerably after successful allogeneic HSCT [53, 65]. Notably, it may take more than 3.5 years for reversal of phenotype and full immune reconstitution of B, NK, and monocyte populations [66]. This may be especially problematic with delayed engraftment typical of umbilical cord grafts. Both PAP and PAH also respond well to HSCT and repeated lung infections or declining lung function

should be considered an indication in clinical context [53]. Earlier transplantation, before organ dysfunction ensues, results in less morbidity and mortality.

MDS/AML

Allogeneic HCT remains the only treatment with favorable responses in *GATA2*-mutated MDS/AML (Fig. 3). In the NIH experience, 21 patients were transplanted for either hematological (MDS/AML) or immunological indications (age 15–49 years) with good responses (Fig. 1). Of note, half the patients who were not transplanted passed away by age 40 [51]. A similar NIH experience further outlined use of conditioning regimens for non-myeloablative allogeneic HCT [66]. Donors included fully matched related and unrelated donors (conditioning-fludarabine + total body radiation 200 cGy) and alternative sources such as umbilical cord blood and haploidentical bone marrow (fludarabine + cyclophosphamide and total body irradiation 200 cGy, with posttransplant cyclophosphamide for T-cell replete grafts). Busulfan was later added for a more robust eradication of the *GATA2* clone. Azithromycin was started before and continued for 1 year posttransplant due to increased propensity to nontuberculous mycobacterial (NTM) infections, in addition to standard prophylaxis. No NTM infections during or after transplant were reported using prophylaxis. Overall survival was 57% at 36 months. Our patient characteristics and outcomes are shown in Table 2. Tacrolimus was used for graft versus host disease prophylaxis. All four patients have engrafted with 100% donor chimerisms (CD3 and CD33 fractions). One patient had CMV-Cytomegalovirus reactivation and refractory thrombocytopenia which failed to improve despite splenectomy. Three developed acute GVHD and one had chronic GVHD involving esophagus with dysphagia and strictures that improved with steroids.

Two clinical trials are currently recruiting patients for myeloablative and reduced-intensity conditioning allogeneic HSCT for *GATA2* mutations and enrollment is encouraged whenever feasible (NCT01861106 and NCT00923364 at www.clinicaltrails.gov).

Genetic counseling

Early genetic diagnosis and screening is paramount [53]. Patients and families should be seen in conjunction with a geneticist. Suggested screening categories are listed in Table 3. Variable phenotypes resulting from different GATA2 mutations are listed in Table 4.

Conflicts of Interest

None declared.

References

1. Simon, M. C. 1995. Gotta have GATA. Nat. Genet. 11:9–11.
2. Bresnick, E. H., K. R. Katsumura, H. Y. Lee, K. D. Johnson, and A. S. Perkins. 2012. Master regulatory GATA transcription factors: mechanistic principles and emerging links to hematologic malignancies. Nucleic Acids Res. 40:5819–5831.
3. Pevny, L., M. C. Simon, E. Robertson, W. H. Klein, S. F. Tsai, V. D'Agati, et al. 1991. Erythroid differentiation in chimaeric mice blocked by a targeted mutation in the gene for transcription factor GATA-1. Nature 349:257–260.
4. Simon, M. C., L. Pevny, M. V. Wiles, G. Keller, F. Costantini, and S. H. Orkin. 1992. Rescue of erythroid development in gene targeted GATA-1- mouse embryonic stem cells. Nat. Genet. 1:92–98.
5. Weiss, M. J., and S. H. Orkin. 1995. Transcription factor GATA-1 permits survival and maturation of erythroid precursors by preventing apoptosis. Proc. Natl. Acad. Sci. USA 92:9623–9627.
6. Fujiwara, Y., C. P. Browne, K. Cunniff, S. C. Goff, and S. H. Orkin. 1996. Arrested development of embryonic red cell precursors in mouse embryos lacking transcription factor GATA-1. Proc. Natl. Acad. Sci. USA 93:12355–12358.
7. Yu, C., A. B. Cantor, H. Yang, C. Browne, R. A. Wells, Y. Fujiwara, et al. 2002. Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage in vivo. J. Exp. Med. 195:1387–1395.
8. Orkin, S. H., R. A. Shivdasani, Y. Fujiwara, and M. A. McDevitt. 1998. Transcription factor GATA-1 in megakaryocyte development. Stem Cells 16(Suppl. 2):79–83.
9. Caldwell, J. T., H. Edwards, A. A. Dombkowski, S. A. Buck, L. H. Matherly, Y. Ge, et al. 2013. Overexpression of GATA1 confers resistance to chemotherapy in acute megakaryocytic leukemia. PLoS One 8:e68601.
10. Cabelof, D. C., H. V. Patel, Q. Chen, H. van Remmen, L. H. Matherly, Y. Ge, et al. 2009. Mutational spectrum at GATA1 provides insights into mutagenesis and leukemogenesis in Down syndrome. Blood 114:2753–2763.
11. Vicente, C., A. Conchillo, M. A. Garcia-Sanchez, and M. D. Odero. 2012. The role of the GATA2 transcription factor in normal and malignant hematopoiesis. Crit. Rev. Oncol. Hematol. 82:1–17.
12. Harigae, H. 2006. GATA transcription factors and hematological diseases. Tohoku J. Exp. Med. 210:1–9.
13. Ling, K. W., K. Ottersbach, J. P. van Hamburg, A. Oziemlak, F. Y. Tsai, S. H. Orkin, et al. 2004. GATA-2 plays two functionally distinct roles during the ontogeny of hematopoietic stem cells. J. Exp. Med. 200:871–882.
14. Tsai, F. Y., G. Keller, F. C. Kuo, M. Weiss, J. Chen, M. Rosenblatt, et al. 1994. An early haematopoietic defect in

mice lacking the transcription factor GATA-2. Nature 371:221–226.

15. Tsai, F. Y., and S. H. Orkin. 1997. Transcription factor GATA-2 is required for proliferation/survival of early hematopoietic cells and mast cell formation, but not for erythroid and myeloid terminal differentiation. Blood 89:3636–3643.

16. Hahn, C. N., C. E. Chong, C. L. Carmichael, E. J. Wilkins, P. J. Brautigan, X. C. Li, et al. 2011. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat. Genet. 43:1012–1017.

17. Kazenwadel, J., G. A. Secker, Y. J. Liu, J. A. Rosenfeld, R. S. Wildin, J. Cuellar-Rodriguez, et al. 2012. Loss-of-function germline GATA2 mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature. Blood 119:1283–1291.

18. Bodor, C., A. Renneville, M. Smith, A. Charazac, S. Iqbal, P. Etancelin, et al. 2012. Germ-line GATA2 p.THR354MET mutation in familial myelodysplastic syndrome with acquired monosomy 7 and ASXL1 mutation demonstrating rapid onset and poor survival. Haematologica 97:890–894.

19. Bresnick, E. H., H. Y. Lee, T. Fujiwara, K. D. Johnson, and S. Keles. 2010. GATA switches as developmental drivers. J. Biol. Chem. 285:31087–31093.

20. Visvader, J. E., M. Crossley, J. Hill, S. H. Orkin, and J. M. Adams. 1995. The C-terminal zinc finger of GATA-1 or GATA-2 is sufficient to induce megakaryocytic differentiation of an early myeloid cell line. Mol. Cell. Biol. 15:634–641.

21. Chou, S. T., E. Khandros, L. C. Bailey, K. E. Nichols, C. R. Vakoc, Y. Yao, et al. 2009. Graded repression of PU.1/Sfpi1 gene transcription by GATA factors regulates hematopoietic cell fate. Blood 114:983–994.

22. de Pater, E., P. Kaimakis, C. S. Vink, T. Yokomizo, T. Yamada-Inagawa, R. van der Linden, et al. 2013. Gata2 is required for HSC generation and survival. J. Exp. Med. 210:2843–2850.

23. Pai, S. Y., M. L. Truitt, C. N. Ting, J. M. Leiden, L. H. Glimcher, and I. C. Ho. 2003. Critical roles for transcription factor GATA-3 in thymocyte development. Immunity 19:863–875.

24. Ting, C. N., M. C. Olson, K. P. Barton, and J. M. Leiden. 1996. Transcription factor GATA-3 is required for development of the T-cell lineage. Nature 384:474–478.

25. Kim, P. J., S. Y. Pai, M. Brigl, G. S. Besra, J. Gumperz, and I. C. Ho. 2006. GATA-3 regulates the development and function of invariant NKT cells. J. Immunol. 177:6650–6659.

26. Pai, S. Y., B. Y. Kang, A. M. Sabadini, E. Parisini, M. L. Truitt, and I. C. Ho. 2008. Distinct structural requirements of GATA-3 for the regulation of thymocyte and Th2 cell differentiation. J. Immunol. 180:1050–1059.

27. Pai, S. Y., M. L. Truitt, and I. C. Ho. 2004. GATA-3 deficiency abrogates the development and maintenance of T helper type 2 cells. Proc. Natl. Acad. Sci. USA 101:1993–1998.

28. Tai, T. S., S. Y. Pai, and I. C. Ho. 2013. GATA-3 regulates the homeostasis and activation of CD8+ T cells. J. Immunol. 190:428–437.

29. Shaw-Smith, C., E. De Franco, H. L. Allen, M. Batlle, S. E. Flanagan, M. Borowiec, et al. 2014. GATA4 mutations are a cause of neonatal and childhood-onset diabetes. Diabetes 63:2888–2894.

30. Peters, I., N. Dubrowinskaja, M. Kogosov, M. Abbas, J. Hennenlotter, C. von Klot, et al. 2014. Decreased GATA5 mRNA expression associates with CpG island methylation and shortened recurrence-free survival in clear cell renal cell carcinoma. BMC Cancer 14:101.

31. Bagu, E. T., A. Layoun, A. Calve, and M. M. Santos. 2013. Friend of GATA and GATA-6 modulate the transcriptional up-regulation of hepcidin in hepatocytes during inflammation. Biometals 26:1051–1065.

32. van Berlo, J. H., B. J. Aronow, and J. D. Molkentin. 2013. Parsing the roles of the transcription factors GATA-4 and GATA-6 in the adult cardiac hypertrophic response. PLoS One 8:e84591.

33. Laforest, B., and M. Nemer. 2011. GATA5 interacts with GATA4 and GATA6 in outflow tract development. Dev. Biol. 358:368–378.

34. Molkentin, J. D. 2000. The zinc finger-containing transcription factors GATA-4, -5, and -6. Ubiquitously expressed regulators of tissue-specific gene expression. J. Biol. Chem. 275:38949–38952.

35. Grigorakaki, C., F. Morceau, S. Chateauvieux, M. Dicato, and M. Diederich. 2011. Tumor necrosis factor alpha-mediated inhibition of erythropoiesis involves GATA-1/GATA-2 balance impairment and PU.1 over-expression. Biochem. Pharmacol. 82:156–166.

36. Kitajima, K., M. Tanaka, J. Zheng, H. Yen, A. Sato, D. Sugiyama, et al. 2006. Redirecting differentiation of hematopoietic progenitors by a transcription factor, GATA-2. Blood 107:1857–1863.

37. Walsh, J. C., R. P. DeKoter, H. J. Lee, E. D. Smith, D. W. Lancki, M. F. Gurish, et al. 2002. Cooperative and antagonistic interplay between PU.1 and GATA-2 in the specification of myeloid cell fates. Immunity 17:665–676.

38. Zhang, P., G. Behre, J. Pan, A. Iwama, N. Wara-Aswapati, H. S. Radomska, et al. 1999. Negative cross-talk between hematopoietic regulators: GATA proteins repress PU.1. Proc. Natl. Acad. Sci. USA 96:8705–8710.

39. Grossmann, V., C. Haferlach, N. Nadarajah, A. Fasan, S. Weissmann, A. Roller, et al. 2013. CEBPA double-mutated acute myeloid leukaemia harbours concomitant molecular mutations in 76.8% of cases with TET2 and GATA2

alterations impacting prognosis. Br. J. Haematol. 161:649–658.

40. Mandoli, A., A. A. Singh, P. W. Jansen, A. T. Wierenga, H. Riahi, G. Franci, et al. 2013. CBFB-MYH11/RUNX1 together with a compendium of hematopoietic regulators, chromatin modifiers and basal transcription factors occupies self-renewal genes in inv(16) acute myeloid leukemia. Leukemia 28:770–778.

41. Nottingham, W. T., A. Jarratt, M. Burgess, C. L. Speck, J. F. Cheng, S. Prabhakar, et al. 2007. Runx1-mediated hematopoietic stem-cell emergence is controlled by a Gata/Ets/SCL-regulated enhancer. Blood 110:4188–4197.

42. Tijssen, M. R., A. Cvejic, A. Joshi, R. L. Hannah, R. Ferreira, A. Forrai, et al. 2011. Genome-wide analysis of simultaneous GATA1/2, RUNX1, FLI1, and SCL binding in megakaryocytes identifies hematopoietic regulators. Dev. Cell 20:597–609.

43. Wilson, N. K., R. T. Timms, S. J. Kinston, Y. H. Cheng, S. H. Oram, J. R. Landry, et al. 2010. Gfi1 expression is controlled by five distinct regulatory regions spread over 100 kilobases, with Scl/Tal1, Gata2, PU.1, Erg, Meis1, and Runx1 acting as upstream regulators in early hematopoietic cells. Mol. Cell. Biol. 30:3853–3863.

44. Hsu, A. P., E. P. Sampaio, J. Khan, K. R. Calvo, J. E. Lemieux, S. Y. Patel, et al. 2011. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. Blood 118:2653–2655.

45. Camargo, J. F., S. A. Lobo, A. P. Hsu, C. S. Zerbe, G. P. Wormser, and S. M. Holland. 2013. MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. Clin. Infect. Dis. 57:697–699.

46. Vinh, D. C., S. Y. Patel, G. Uzel, V. L. Anderson, A. F. Freeman, K. N. Olivier, et al. 2010. Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. Blood 115:1519–1529.

47. Ishida, H., K. Imai, K. Honma, S. Tamura, T. Imamura, M. Ito, et al. 2012. GATA-2 anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia. Eur. J. Pediatr. 171:1273–1276.

48. Ostergaard, P., M. A. Simpson, F. C. Connell, C. G. Steward, G. Brice, W. J. Woollard, et al. 2011. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). Nat. Genet. 43:929–931.

49. Hsu, A. P., K. D. Johnson, E. L. Falcone, R. Sanalkumar, L. Sanchez, D. D. Hickstein, et al. 2013. GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome. Blood 121:3830–3837.

50. Dickinson, R. E., H. Griffin, V. Bigley, L. N. Reynard, R. Hussain, M. Haniffa, et al. 2011. Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. Blood 118:2656–2658.

51. Leiding, J. W., and S. M. Holland. 2012. Warts and all: human papillomavirus in primary immunodeficiencies. J. Allergy Clin. Immunol. 130:1030–1048.

52. Lasbury, M. E., X. Tang, P. J. Durant, and C. H. Lee. 2003. Effect of transcription factor GATA-2 on phagocytic activity of alveolar macrophages from Pneumocystis carinii-infected hosts. Infect. Immun. 71:4943–4952.

53. Spinner, M. A., L. A. Sanchez, A. P. Hsu, P. A. Shaw, C. S. Zerbe, K. R. Calvo, et al. 2013. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics and immunity. Blood 123:809–821.

54. Lim, K. C., T. Hosoya, W. Brandt, C. J. Ku, S. Hosoya-Ohmura, S. A. Camper, et al. 2012. Conditional Gata2 inactivation results in HSC loss and lymphatic mispatterning. J. Clin. Invest. 122:3705–3717.

55. Vicente, C., I. Vazquez, A. Conchillo, M. A. Garcia-Sanchez, N. Marcotegui, O. Fuster, et al. 2012. Overexpression of GATA2 predicts an adverse prognosis for patients with acute myeloid leukemia and it is associated with distinct molecular abnormalities. Leukemia 26:550–554.

56. Ayala, R. M., J. Martinez-Lopez, E. Albizua, A. Diez, and F. Gilsanz. 2009. Clinical significance of Gata-1, Gata-2, EKLF, and c-MPL expression in acute myeloid leukemia. Am. J. Hematol. 84:79–86.

57. West, R. R., A. P. Hsu, S. M. Holland, J. Cuellar-Rodriguez, and D. D. Hickstein. 2013. Acquired ASXL1 mutations are common in patients with inherited GATA2 mutations and correlate with myeloid transformation. Haematologica 99:276–281.

58. Dickinson, R. E., P. Milne, L. Jardine, S. Zandi, S. I. Swierczek, N. McGovern, et al. 2013. The evolution of cellular deficiency in GATA2 mutation. Blood 123:863–874.

59. Zhang, S. J., L. Y. Ma, Q. H. Huang, G. Li, B. W. Gu, X. D. Gao, et al. 2008. Gain-of-function mutation of GATA-2 in acute myeloid transformation of chronic myeloid leukemia. Proc. Natl. Acad. Sci. USA 105:2076–2081.

60. Zhang, S. J., J. Y. Shi, and J. Y. Li. 2009. GATA-2 L359 V mutation is exclusively associated with CML progression but not other hematological malignancies and GATA-2 P250A is a novel single nucleotide polymorphism. Leuk. Res. 33:1141–1143.

61. Fujimaki, S., H. Harigae, T. Sugawara, N. Takasawa, T. Sasaki, and M. Kaku. 2001. Decreased expression of transcription factor GATA-2 in haematopoietic stem cells in patients with aplastic anaemia. Br. J. Haematol. 113:52–57.

62. Wu, X., Y. Li, K. Zhu, Z. Wang, S. Chen, and L. Yang. 2007. GATA-1, -2 and -3 genes expression in bone marrow microenviroment with chronic aplastic anemia. Hematology 12:331–335.

63. Xu, Y., Y. Takahashi, Y. Wang, A. Hama, N. Nishio, H. Muramatsu, et al. 2009. Downregulation of GATA-2 and overexpression of adipogenic gene-PPARgamma in mesenchymal stem cells from patients with aplastic anemia. Exp. Hematol. 37:1393–1399.

64. Pasquet, M., C. Bellanne-Chantelot, S. Tavitian, N. Prade, B. Beaupain, O. Larochelle, et al. 2013. High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia. Blood 121:822–829.

65. Cuellar-Rodriguez, J., J. Gea-Banacloche, A. F. Freeman, A. P. Hsu, C. S. Zerbe, K. R. Calvo, et al. 2011. Successful allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. Blood 118:3715–3720.

66. Grossman, J., J. Cuellar-Rodriguez, J. Gea-Banacloche, C. Zerbe, K. Calvo, T. Hughes, et al. 2014. Nonmyeloablative allogeneic hematopoietic stem-cell transplantation for GATA2 deficiency. Biol. Blood Marrow Transplant. S1083–8791(14):00503–5.

67. Holme, H., U. Hossain, M. Kirwan, A. Walne, T. Vulliamy, and I. Dokal. 2012. Marked genetic heterogeneity in familial myelodysplasia/acute myeloid leukaemia. Br. J. Haematol. 158:242–248.

68. Gimenez-Sanchez, F., E. Cobos-Carrascosa, M. Sanchez-Forte, M. Martinez-Lirola, E. Lopez-Ruzafa, R. Galera-Martinez, et al. 2013. Different penetrance of disseminated infections caused by non-tuberculous mycobacteria in mendelian susceptibility to mycobacterial disease associated with a novel mutation. Pediatr. Infect. Dis. J. 33:328–330.

69. Machaczka, M., F. Lorenz, G. Kleinotiene, A. Bulanda, A. Markuszewska-Kuczynska, J. Raistenskis, et al. 2013. Recurrent pulmonary aspergillosis and mycobacterial infection in an unsplenectomized patient with type 1 Gaucher disease. Ups. J. Med. Sci. 119:44–49.

70. Quispel, W. T., J. A. Stegehuis-Kamp, S. J. Santos, A. van Wengen, E. Dompeling, R. M. Egeler, et al. 2013. Intact IFN-gammaR1 expression and function distinguishes Langerhans cell histiocytosis from mendelian susceptibility to mycobacterial disease. J. Clin. Immunol. 34:600.

71. Alders, M., A. Mendola, L. Ades, L. Al Gazali, C. Bellini, B. Dallapiccola, et al. 2013. Evaluation of clinical manifestations in patients with severe lymphedema with and without CCBE1 mutations. Mol. Syndromol. 4:107–113.

72. Edeer Karaca, N., S. Boisson-Dupuis, G. Aksu, J. Bustamante, G. Kandiloglu, N. Ozsan, et al. 2012. Granulomatous skin lesions, severe scrotal and lower limb edema due to mycobacterial infections in a child with complete IFN-gamma receptor-1 deficiency. Immunotherapy 4:1121–1127.

73. Gordon, K., D. Schulte, G. Brice, M. A. Simpson, M. G. Roukens, A. van Impel, et al. 2013. Mutation in vascular endothelial growth factor-C, a ligand for vascular endothelial growth factor receptor-3, is associated with autosomal dominant milroy-like primary lymphedema. Circ. Res. 112:956–960.

74. Itoh, M., and H. Nakagawa. 2013. A novel complex insertion-deletion mutation in the FOXC2 gene in a Japanese patient with Lymphedema-Distichiasis Syndrome. Eur. J. Dermatol. 23:411–413.

75. Mendola, A., M. J. Schlogel, A. Ghalamkarpour, A. Irrthum, H. L. Nguyen, E. Fastre, et al. 2013. Mutations in the VEGFR3 signaling pathway explain 36% of familial lymphedema. Mol. Syndromol. 4:257–266.

76. Shah, S., L. K. Conlin, L. Gomez, O. Aagenaes, K. Eiklid, A. S. Knisely, et al. 2013. CCBE1 mutation in two siblings, one manifesting lymphedema-cholestasis syndrome, and the other, fetal hydrops. PLoS One 8:e75770.

77. Tanaka, T., N. Motoi, Y. Tsuchihashi, R. Tazawa, C. Kaneko, T. Nei, et al. 2011. Adult-onset hereditary pulmonary alveolar proteinosis caused by a single-base deletion in CSF2RB. J. Med. Genet. 48:205–209.

78. Hyde, R. K., and P. P. Liu. 2011. GATA2 mutations lead to MDS and AML. Nat. Genet. 43:926–927.