Annals of Hematology (2018) 97:1961–1973
https://doi.org/10.1007/s00277-018-3388-4

ORIGINAL ARTICLE

Allogeneic hematopoietic cell transplantation in patients with *GATA2* deficiency—a case report and comprehensive review of the literature

Alexander Simonis[1] · Michaela Fux[2] · Gayathri Nair[1] · Nicolas J. Mueller[3] · Eugenia Haralambieva[4] · Thomas Pabst[5] · Jana Pachlopnik Schmid[6] · Adrian Schmidt[7] · Urs Schanz[1] · Markus G Manz[1] · Antonia M. S. Müller[1]

Received: 10 April 2018 / Accepted: 27 May 2018 / Published online: 13 June 2018

Abstract

Recently, an immunodeficiency syndrome caused by guanine-adenine-thymine-adenine 2 (*GATA2*) deficiency has been described. The syndrome is characterized by (i) typical onset in early adulthood, (ii) profound peripheral blood cytopenias of monocytes, B lymphocytes, and NK cells, (iii) distinct susceptibility to disseminated non-tuberculous mycobacterial (NTM) and other opportunistic infections (particularly human papillomavirus), and (iv) a high risk of developing hematologic malignancies (myelodysplastic syndromes (MDS); acute myeloid leukemias (AML)). Considerable clinical heterogeneity exists among patients with *GATA2* deficiency, but once infectious symptoms occur or MDS/AML arises, survival declines significantly. Allogeneic hematopoietic cell transplantation (HCT) currently provides the only curative treatment option for both MDS/AML and dysfunctional immunity with life-threatening opportunistic infections. Strategies regarding timing of allogeneic HCT, antimicrobial prophylaxis and treatment, intensity of the preparative regimen, and optimal donor and graft source have not been clearly defined due to the rarity of the disease. Here, we provide a comprehensive analysis of the available literature and published case reports on the use of allogeneic HCT in patients with *GATA2* deficiency. In addition, a case of a young woman with *GATA2* deficiency, who developed an immune reconstitution inflammatory syndrome in her mycobacterial skin lesions post allogeneic HCT is presented and illustrates distinct problems encountered in this disease context.

Keywords *GATA2* deficiency · Allogeneic hematopoietic cell transplantation · Immune reconstitution inflammatory syndrome · Myelodysplastic syndrome

Introduction

Guanine-adenine-thymine-adenine 2 (*GATA2*) deficiency has been identified as the genetic origin to a multifarious disease involving a spectrum of hematologic and non-hematologic anomalies. The most common features are cytopenias, immunodeficiency with increased susceptibility to opportunistic infections, and a high risk of developing myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML) [1, 2].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3388-4) contains supplementary material, which is available to authorized users.

✉ Antonia M. S. Müller
AntoniaMaria.Mueller@usz.ch

[1] Division of Hematology, University and University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland

[2] Center of Laboratory Medicine, University Hospital, Inselspital Bern, CH-3010 Bern, Switzerland

[3] Division of Infectious Diseases and Hospital Epidemiology, University and University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland

[4] Department of Pathology, University and University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland

[5] Department of Medical Oncology, University Hospital, Inselspital Bern, CH-3010 Bern, Switzerland

[6] Pediatric Immunology, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland

[7] Department of Internal Medicine, Division of Medical Oncology and Hematology, City Hospital Triemli, Birmensdorferstrasse 497, CH-8063 Zurich, Switzerland

In 2010, Vinh et al. reported on a series of 18 patients, of which 14 suffered from infections with mycobacteria and human papillomavirus (HPV); in addition, 5 patients had fungal complications, predominantly histoplasmosis and molds. Of these 18 patients, 10 developed malignancies, specifically myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML), and 5 patients displayed signs of pulmonary alveolar proteinosis (PAP) [3]. At that time, this distinct clinical syndrome was identified by patient history and routine laboratory work-up and was, because of the characteristic monocytopenia and frequent *Mycobacterium avium* complex (MAC) infections, referred to as MonoMAC syndrome [4]. Remarkably, among the first cohort of 18 patients in five families, several generations were affected, suggesting that the syndrome could be obtained by both autosomal dominant transmission or arise sporadically [3]. To unravel the genetic origin of *dendritic cell* (DC), *monocyte*, *B* and *natural killer* (NK) *lymphoid* (DCML) *deficiency*, a similar recently described syndrome [5], Dickinson et al. performed exome sequencing in four affected patients and identified only one gene, *GATA2*, to carry mutations in all examined unrelated individuals [6]. The finding that *GATA2* is also the key player in the pathophysiology of MonoMAC syndrome was confirmed soon after when 12 distinct mutations in *GATA2* were detected in 20 patients and relatives with this syndrome [7]. Further, mutations in *GATA2* were identified to underlie Emberger syndrome, a syndrome that encompasses the co-occurrence of primary lymphedema with MDS/AML, often in association with abnormalities in lymphocyte subsets, immune dysfunction with widespread cutaneous warts, and sensorineural deafness [8]. In the same year, the association between heritable *GATA2* mutations and familial MDS/AML was discovered [9]. Later, reports on cutaneous manifestations, including erythema nodosum-like inflammatory nodules, erythematous papules and indurated plaques with a histology presenting as panniculitis or granulomatous inflammation without microorganisms, which occasionally were accompanied by fever and arthralgias, have been added to the literature [10, 11]. Altogether, it has become clear that *GATA2* deficiency is a single genetic protean disease with a wide spectrum of hematologic and non-hematologic anomalies that can vary greatly in severity and range of clinical symptoms. Most importantly, however, *GATA2* deficiency predisposes patients to MDS/AML, which makes the disease a life-threatening condition (Fig. 1) [10].

In 2014, Spinner et al. reported on a large cohort of patients of various ethnic backgrounds (75% white, 16% Hispanic, 7% Afro-American, 2% Asian) with *GATA2* deficiency referred to the National Institutes of Health (NIH). Forty of the 57 patients were identified based on clinical presentation, mostly severe viral (32% of patients) or non-tuberculous mycobacterial (NTM; 28%) infections, MDS/AML (21%), lymphedema (9%), fungal infections (4%), or PAP. The other 17 patients

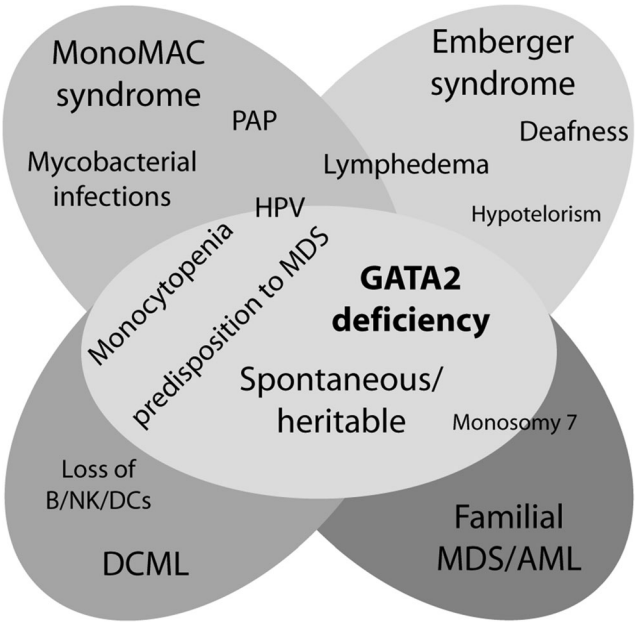


Fig. 1 Key clinical findings in MonoMAC syndrome, familial MDS/AML, dendritic cell, monocyte, and B and NK lymphoid deficiency (*DCML*) and Emberger syndrome that are all caused a germline *GATA2* mutation

were identified through screening of family members. The median age of initial clinical manifestation was 20 years with a wide age range from early childhood to late adulthood [1].

Analyzing datasets and stored material for genetic testing from the database of the European Working Group of MDS in childhood (EWOG-MDS) that were collected over a period of 15 years, Wlodarski et al. reported in 2016 that germline *GATA2* mutations accounted for 15% of advanced and 7% of all primary cases of pediatric MDS. Of the 508 patients tested, 57 MDS patients had germline *GATA2* mutations. Prevalence of *GATA2* mutations was particularly high in those MDS patients with monosomy 7 (37% of all patients with monosomy 7), reaching a peak in adolescence (72% of adolescents with monosomy 7). In fact, this study identified *GATA2* as the most common germline defect predisposing to pediatric MDS. Within this group of patients with *GATA2* deficiency, 39% presented with immunodeficiency, 23% with lymphedema/hydrocele, and 9% with deafness. Moreover, anomalies of the urogenital tract and behavioral problems (e.g., autism and aggressive behavior) were reported as novel clinical features recurrently present in the investigated cohort in 12 and in 19% of patients with *GATA2* mutations, respectively [12].

In contrast to most congenital immunodeficiency syndromes, individuals with *GATA2* deficiency typically have normal blood counts during early childhood. Bone marrow samples of patients with *GATA2* deficiency typically are hypocellular, and when they develop MDS, they frequently show multi-lineage dysplasia with atypical megakaryocytes in > 90% and abnormal plasma cells in half of the patients [1, 4,

7]. Once cytopenias develop, these may exist for prolonged periods of time before clinical symptoms manifest, mostly with opportunistic infections, and the diagnosis is established [7]. *GATA2* deficiency is characteristically associated with profoundly decreased or absent counts of monocytes, dendritic cells (DC), natural killer (NK; both $CD56^{bright}$ and to a lesser degree $CD56^{dim}$ subpopulations), and B cells in the blood [1, 3, 13]. In contrast to blood DCs, epidermal Langerhans cells (but not dermal $CD14^{+}CD1a^{+}$ DC), tissue macrophages, and plasma cells appear to be preserved at sites of inflammation and immunoglobulin levels are mostly normal [2, 3, 5].

Increased susceptibility to infections with intracellular pathogens is likely a consequence of macrophage/monocyte dysfunction. Likewise, reduced phagocytic activity of pulmonary alveolar macrophages resulting from *GATA2* deficiency contributes to the common occurrence of pulmonary alveolar proteinosis (PAP) that can be observed in patients with *GATA2* deficiency [14]. The high frequency of human papilloma virus (HPV) and other viral infections results most likely from the profound absence of NK cells [7].

Preemptively, or with disease progression and diagnosis of MDS/AML, the indication for allogeneic hematopoietic cell transplantation (HCT) is given, as this approach provides the only long-term curative treatment for an otherwise often fatal disease. While allogeneic HCT can cure MDS/AML, the management of patients differs substantially during and following allogeneic HCT, as patients enter the procedure with active, often uncontrolled infections, which may persist and need to be controlled during the months to years of severe immunosuppression following the allogeneic HCT procedure.

As *GATA2* deficiencies are rare disease entities that only recently have been recognized, reports on outcomes and complications following allogeneic HCT are scarce and exist mostly in form of case reports or small case series. Here, we searched the literature and provide a comprehensive overview of reports on patients given allogeneic HCTs for *GATA2* deficiency. In addition, we present another clinical case to illustrate the practical difficulties encountered during allogeneic HCT and describe a pronounced immune reconstitution inflammatory phenomenon in this context.

Methods

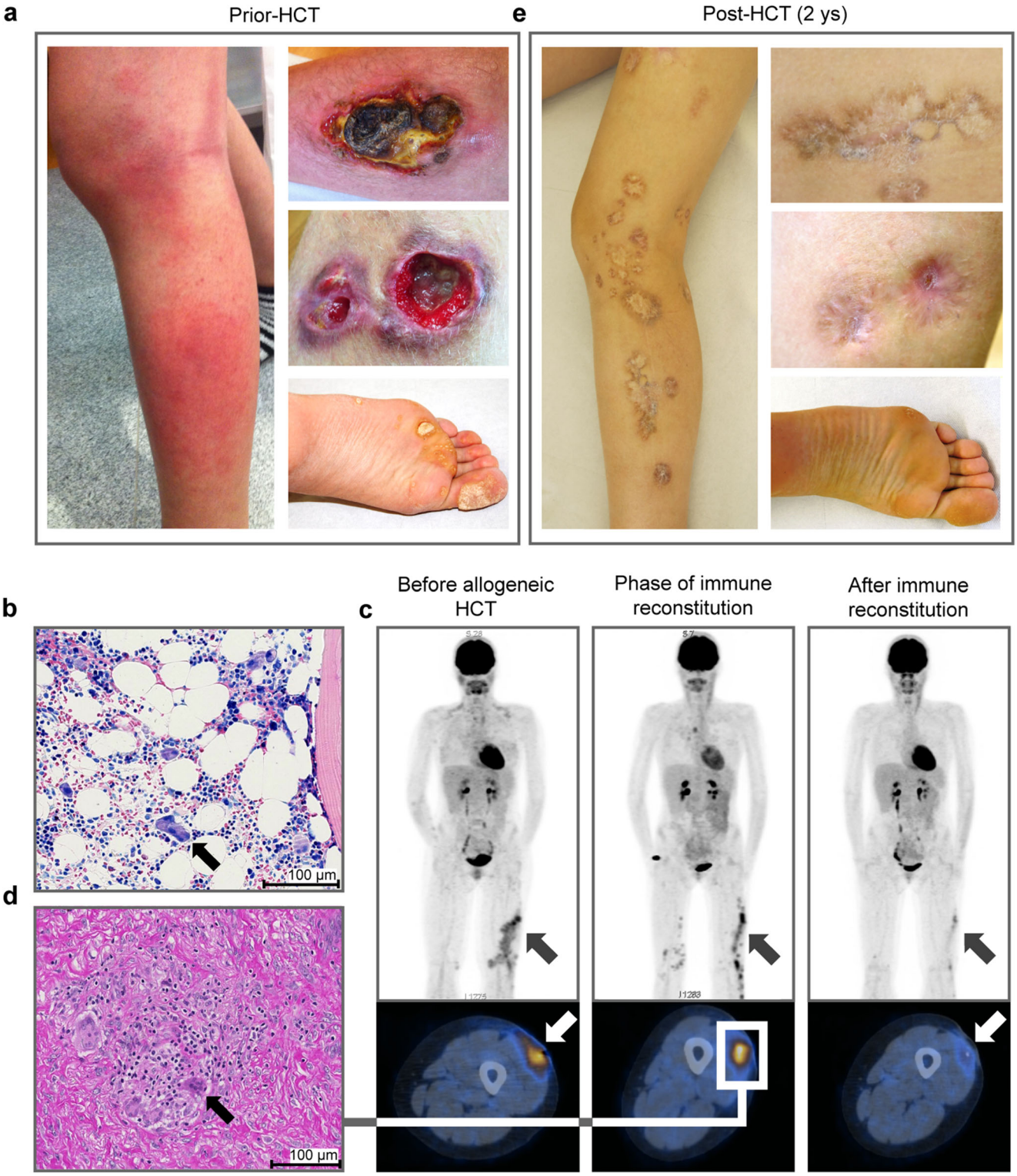
We conducted a systematic review to analyze the available literature on the use and outcomes of allogeneic hematopoietic cell transplantations (HCT) in patients with confirmed *GATA2* deficiency. The analysis was performed using PubMed (http://www.ncbi.nlm.nih.gov) of the National Center for Biotechnology Information, National Library of Medicine of the National Institutes of Health, and Scopus (http://www.scopus.com). Reports from January 2010 until March 2018 were included. The search included the terms "*GATA2* deficiency" and "*GATA2* hematopoietic cell transplantation" as well as the *GATA2* deficiency-associated diseases like "familial myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML)," "dendritic cell, monocyte, B and NK lymphoid deficiency (DCML)," "Monocytopenia and mycobacterial infection (MonoMAC) syndrome," and primary lymphedema associated with predisposition to acute myeloid leukemia ("Emberger syndrome"). Data on age, sex, *GATA2* mutations, symptoms, bone marrow morphology, cytogenetics, HCT-related details, and outcomes were comprehensively summarized using information as provided by the authors.

The patient described in this manuscript provided her informed consent; procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Case report

Here, we present a 17-year-old woman with prolonged history of severe infectious complications, particularly disseminated *Mycobacterium abscessus* infections manifesting as multiple ulcerated skin lesions and involvement of mediastinal lymph nodes. From early childhood on, the patient had contracted numerous warts (*Verruca vulgares*) on hands and feet (Fig. 2a). Further, she suffered from recurrent upper respiratory tract infections, pneumonia with sepsis, and several episodes of otitis media during childhood. When the patient was 16 years old, the clinical course was complicated by symptomatic pulmonary embolism, which was interpreted as unprovoked. The CT scan also revealed evidence of interstitial pneumopathy, suggesting the presence of pulmonary alveolar proteinosis (PAP). PAP, however, was not confirmed as PAS staining of bronchoalveolar lavage (BAL) fluid turned out negative. Also, there was no evidence of PAP in the pre-HCT CT scan. Around the same time, the patient developed lymphedema of the lower extremity. One year later, at age 17, the patient developed cytopenias (hemoglobin 106 g/l, thrombocytes 148 G/l, leukocytes 3.2 G/l, ANC 2.64 G/l, monocytes 0.016 G/l, lymphocytes 0.53 G/l) (Fig. 3a). Analysis of lymphocyte subpopulation by flow cytometry showed reduced counts of B, NK, and $CD4^{+}$ and $CD8^{+}$ T cells; monocytes and blood dendritic cells were completely lacking (Fig. 3a–d). Bone marrow examination revealed the diagnosis of MDS (WHO 2008 refractory cytopenia with multi-lineage dysplasia (RCMD); WHO 2016 MDS with multi-lineage dysplasia (MDS-MLD)) (Fig. 2b) without cytogenetic aberrations (as assessed by karyogram and FISH) and no evidence of *AML1-ETO*, *CBFb-MYH11*, *FLT3-ITD*, *PML-RARa*, and



TCRg rearrangements (as assessed by PCR) or *NPM1* mutation (assessed by sequencing). Detection of a *GATA2* mutation (1045T>G C349G) by PCR confirmed the diagnosis of a MonoMAC syndrome/*GATA2* deficiency. There was no family history of similarly affected patients, suggesting the mutation was acquired rather than inherited.

The patient was referred to our center for upfront allogeneic HCT without prior induction chemotherapy. At that time, she had ongoing disseminated and ulcerated *Mycobacterium abscessus* lesions of the skin (Fig. 2a), which were clinically stable and controlled under therapy with clarithromycin, but still had detectable mycobacteria by PCR. Prior to allogeneic

◀ **Fig. 2** Clinical manifestations. **a** Pre-HCT, images of mycobacterial skin and soft tissue lesions of the leg (right panel top: ulcerated skin lesion; right panel middle: wound healing after surgical intervention; right panel bottom: HPV-associated plantar warts). **b** H&E staining of bone marrow biopsy at diagnosis of MDS, displaying characteristic dysplastic megakaryocytes (arrow). **c** 18F-FDG-PET-CT scans before HCT (left), in the phase of immune reconstitution (middle), and after complete resolution of inflammation /IRIS (right). Arrows indicate areas with increased metabolic activity due to chronic mycobacterial infection (left) and due to immune reconstitution inflammation (middle). **d** H&E staining of an inflamed subcutaneous lesion of the upper leg during immune reconstitution revealing a focal acute and chronic granulomatous, ulcerating inflammation/immune response with giant cells (arrow) without evidence of persistent mycobacteria. **e** 2 years post-HCT, images of healed skin and soft tissue lesions (left side and right panel top images); complete resolution of HPV-associated plantar warts (right panel bottom)

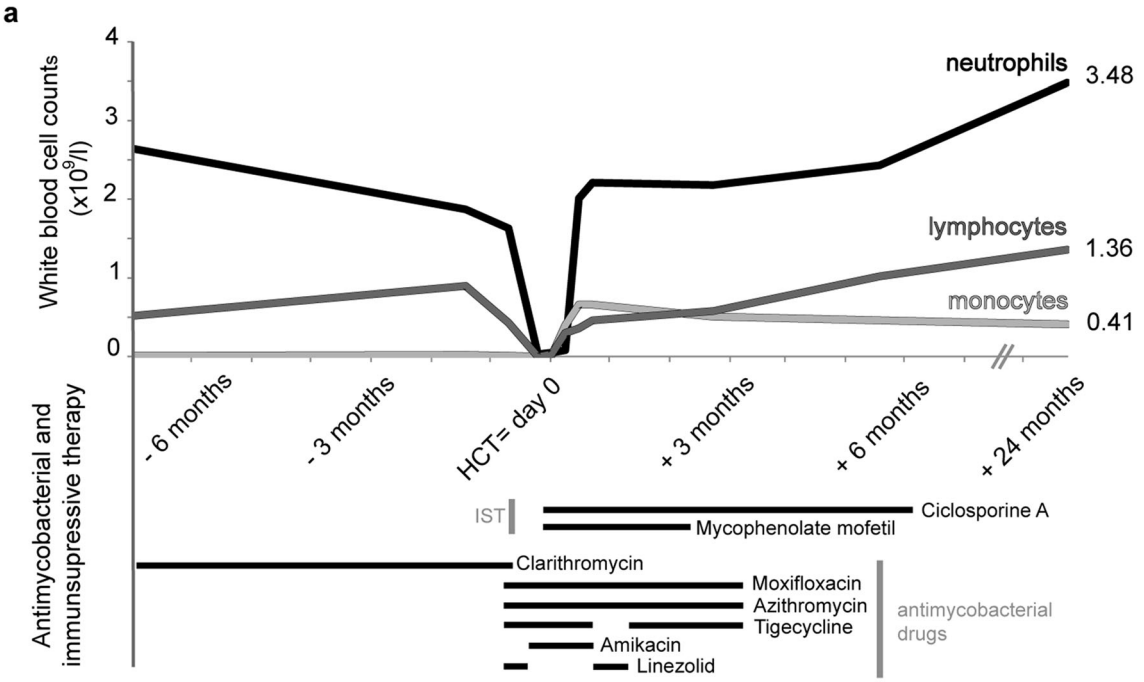
HCT, the anti-infective regimen was escalated with azithromycin, moxifloxacin, linezolid, and tigecyclin to achieve an optimal reduction of the bacterial burden (Fig. 3a). Following a reduced intensity conditioning regimen with fludarabine (30 mg/m^2 day − 7 to − 2) and busulfan (0.8 mg/kg and adjusted to serum levels every 6 h from day − 4 to − 3), 8.12×10^6 CD34$^+$ peripheral blood stem cells/kg body weight from a 10/10 HLA-matched unrelated donor were transplanted. Graft-versus-host disease (GVHD) prophylaxis comprised anti-thymocyte globulin (ATG; 10 mg/kg day − 4 to − 1), cyclosporine A (CSA; starting on day − 4), and mycophenolate mofetil (MMF; starting on day + 1). Antibiotic treatment was continued during the phase of the allogeneic HCT, except linezolid, which was replaced by amikacin due to hemotoxicity of linezolid (Fig. 3a). In addition to the anti-mycobacterial therapy, the patient was treated with meropenem, piperacillin/tazobactam, caspofungin, and valaciclovir because of fever in neutropenia and aphthous stomatitis. After engraftment (on day + 25), the quadruple anti-mycobacterial therapy was reduced to a triple therapy with azithromycin, moxifloxacin, and tigecycline and continued until 14 weeks post-HCT, when antibiotic therapy was stopped (Fig. 3a).

Besides prolonged nausea, diminished appetite, and significant weight loss (13 kg; minimal weight 43.5 kg, BMI 16.0 kg/m^2), the post-HCT course was rather uncomplicated. There were no signs of acute or chronic GVHD. MMF was tapered from day + 54 and stopped on day + 70; CSA was tapered from day + 108 and stopped on day + 208 post-HCT (Fig. 3a). With the reduction and discontinuation of pharmacological immunosuppression, multiple mycobacterial abscesses, which had been visible but clinically stable during and early after HCT, started swelling and appeared inflamed, and the patient complained about pain in these areas. An ^{18}FDG PET-CT scan confirmed increased metabolic activity within the lesions; however, it did not help to clarify whether this inflammation was due to uncontrolled infection or rather immune reconstitution clearing the mycobacterial infection (*immune reconstitution inflammatory syndrome* (*IRIS*)) (Fig. 2c). To better explain the cause of the inflammation and to decide whether to re-initiate antibiotic therapy, a biopsy/excision of a metabolically active skin lesion was obtained (on *d* + 216) for histologic analysis and microbiologic work-up. Histology revealed an inflammatory, chronic granulomatous ulceration (Fig. 2d) without evidence of acid-fast rods (as assessed by Ziehl-Neelsen staining). Likewise, culture and PCR for mycobacteria were negative. With these findings, the process was interpreted as an immune reconstitution phenomenon (IRIS), which lasted over several months. Ultimately, lesions and ulcerations healed and inflammation subsided at approximately 9 months post-HCT. At the same time, the multiple warts on feet and hands (*Verruca vulgares*) disappeared spontaneously (Fig. 2a). Today, 42 months post-allo-HCT, the patient's immune system appears recovered with normal counts of monocytes and B, NK, and CD4$^+$ and CD8$^+$ T cells (Fig. 3a–b), full donor chimerism, no ongoing infections, and no increased susceptibility to infections. Regarding the MDS, the patient has been in an ongoing complete remission since transplantation. The *GATA2* mutation (1045T>G C349G) was no longer detectable in bone marrow or blood following the allogeneic HCT.

Allogeneic hematopoietic cell transplantation in GATA2 deficiencies

Allogeneic HCT represents a potentially curative therapy for the abnormal hematopoietic and lymphoid system of patients with *GATA2* deficiency. However, these patients pose a particular therapeutic challenge due to their disease-associated comorbidities, including life-threatening infections with their respective long-term antimicrobial treatments, pulmonary alveolar proteinosis (PAP) resulting from defective alveolar macrophages, and others. Although allogeneic HCT can reverse the hematologic, immunologic, and to some extend the clinical phenotype, it is not entirely clear who exactly should be candidates for allo-HSCT and when is the best time to perform the procedure. There is a high clinical variability in onset, course, and severity of manifestations with incomplete penetrance and lack of close phenotype-genotype correlation data in *GATA2* deficiency even within families. Thus, not every patient with *GATA2* deficiency may actually require an allogeneic HCT and the benefit of the treatment must outweigh the risks and complications inherent to the procedure, including toxicity of the conditioning regimen, GVHD, uncontrolled infections, and treatment-related mortality. Moreover, optimal conditioning regimen and donor stem cell source remain unclear.

Besides two small prospective studies [15–17] and the two larger analyses mentioned above (EWOG-MDS and NIH [1, 12]), only case reports and small case series describing use and outcomes of allogeneic HCT in patients with *GATA2*



b

	1.5y prior Tx	1.5y post Tx
CD56+ NK-cells	5/μl	127/μl
CD3+ T-cells	496/μl	1180/μl
CD4+ T-cells	83/μl	266/μl
CD8+ T-cells	298/μl	850/μl
CD19+ B-cells	15/μl	355/μl
CD123+ pDCs	0/μl	n/a
CD11c+ mDCs	0/μl	n/a

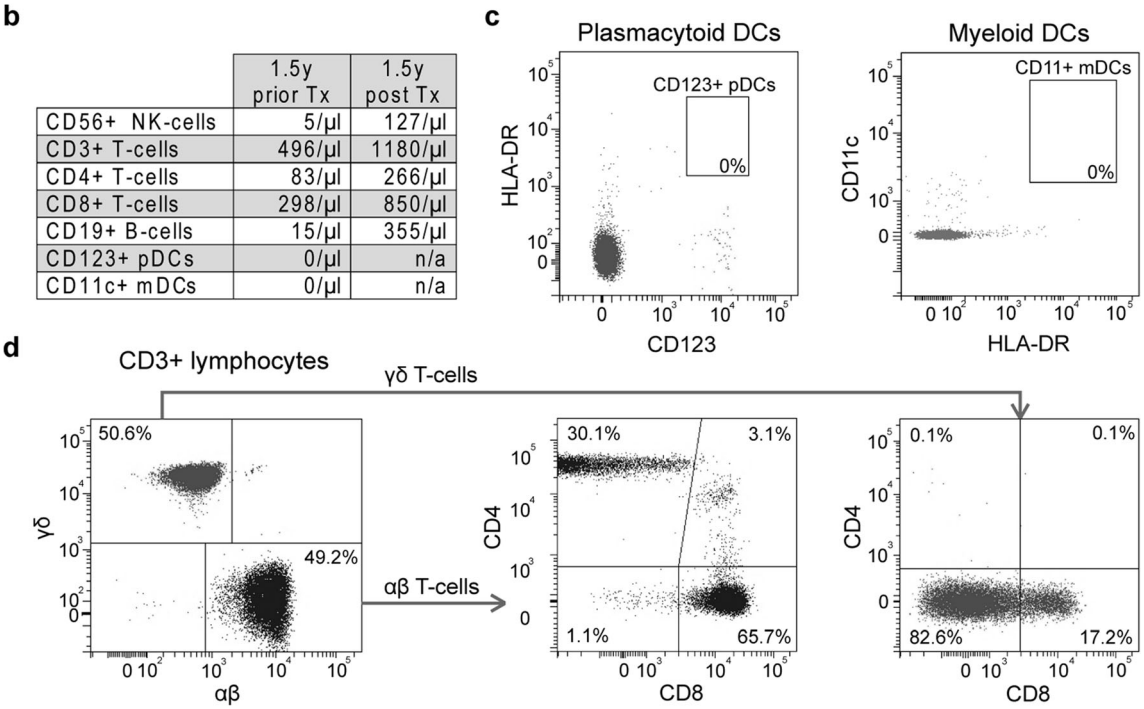


Fig. 3 Blood values, lymphocyte subpopulations, and immunosuppressive/ anti-mycobacterial treatments. **a** Timeline of white blood cell counts (WBC), displaying neutrophils (black), lymphocytes (dark gray), and monocytes (light gray); in addition immunosuppressive (IST) and anti-mycobacterial therapies are displayed. Day zero is the day of graft infusion (HCT). **b** Lymphocyte subpopulations at diagnosis and at 18 months post allogeneic HCT. **c** Representative immunophenotypic plots displaying the lack of $CD123^+$ $HLA\text{-}DR^+$ $lineage^{neg}$ plasmacytoid dendritic cells (DC) (left plot) and $CD11c^+$ $HLA\text{-}DR^+$ $lineage^{neg}$ myeloid DC (right plot) at diagnosis. **d** Representative immunophenotypic plots displaying the distribution of ab and gd subfractions of $CD3^+$ T cells (plot on left side). αβ T cells contained more $CD8^+$ cells with an inverse CD4:CD8 ratio of approximately 0.5 (plot in middle). γδ T cells comprised mostly $CD4^-$ $CD8^-$ double-negative cells (> 80%) and some $CD8^+$ cells (< 20%), but no $CD4^+$ cells (plot on right side)

deficiency exist. Supplemental Table 1 displays patient characteristics, transplant conditions, and outcomes of 183 patients who underwent allogeneic HCT for treatment of genetically proven or highly suggestive *GATA2* deficiency between 2010 and 2018 [2, 3, 5, 8–10, 18–39]. The supplemental text provides a comprehensive description of these published data

Table 1 Compiled patient and treatment characteristics

Total (patients)			183	
	Details provided (*n*)		138	75%
Age		Mean (years)	22.7	
		Median (years)	21	
		Range (years)	4–53	
	n		*n*	%
Sex	137	Female	63	46
		Male	74	54
Symptoms	77	HPV	45	70
		HSV	9	16
		EBV	11	14
		NTM	24	31
		Other infections	38	49
		Lymphedema	14	18
		PAP	7	9
Bone marrow	136	MDS	114	84
		AML/ALL	14	10
		CMML	2	2
		Normal/others	6	4
Cytogenetics	138	Monosomy 7	62	45
		Trisomy 8	21	15
		Other aberrations	28	20
		Normal or not reported	45	33
Conditioning	99	NMA/RIC	29	29
		MAC	70	71
Graft source	111	BM	59	53
		PBSC	46	41
		CB	6	5
Donor	121	MRD	28	23
		MUD	70	58
		Haplo	17	14
		CB	6	5
Complications post-HCT	116	GVHD (total)	46	40
		Acute GVHD	33	28
		Chronic GVHD	14	12
		GVHD (not specified)	9	8
		Infections	26	22
Outcome	130	Alive	99	74
		Died	31	26

sets. Table 1 displays the compiled data on 138 patients with *GATA2* deficiency, in whom more detailed information regarding characteristics, hematologic features, disease, conditioning regimens, graft source, outcomes, and complications are provided by the authors.

The age at transplantation ranged between 4 and 53 years; 46% of patients were females, and 54% were males.

Indication for HCT The vast majority of patients underwent allogeneic HCT with the diagnosis of MDS (84%) or acute leukemias (10%; mostly AML, including one acute lymphoblastic leukemia). There were also transplants performed in patients with CMML (2%) and in patients prior to development of a malignancy but for better management and control of infectious complications (4%).

Conditioning, graft source, donors Of those patients with documented details, approximately one third was prepared with nonmyeloablative or reduced intensity conditioning. Particularly in the earlier years, concerns regarding the

tolerability of the chemotherapy were raised because of active severe infections and often poor clinical condition of the patients. However, using these conditioning regimens, a substantial proportion of engraftment failures and late graft rejections were documented, and therefore, conditioning regimens were intensified. From those patients given myeloablative conditioning, it appears that toxicity is not exceedingly higher compared with patients without *GATA2* deficiency and treatment-related morbidity is manageable. Approximately half of the patients received bone marrow or peripheral stem cell grafts; six patients were given cord blood units. The majority of donors used were matched-unrelated donors (58%), followed by matched-related donors (23%), mismatched related/haploidentical (14%) donors, and cord blood (5%).

Graft-versus-host disease One third of documented patients developed GVHD post-allogeneic HCT (40%), mostly acute GVHD (28%) and less frequently chronic GVHD (12%). This frequency of GVHD appears low, but may also be due to lacking documentation in the case reports and case series. In the phase 1/2 study reported by Grossman et al. 7/14 (57%) had acute GVHD, mostly of the skin. Three of 14 patients developed °III–IV GVHD of two or more organs. [16]. The recent follow-up study using more intensive busulfan-based conditioning revealed a slightly higher rate of °III–IV acute GVHD (26%) in recipients of MRD and MUD grafts, but not in those given haploidentical grafts. Similarly, MRD and MUD recipients had a higher rate of chronic GVHD (46%) compared with recipients of haploidentical grafts (28%) [17]. In most other publications, no detailed information on severity of symptoms, treatment, and response to treatment is given. However, it appears that the proportion of patients developing GVHD is comparable to other transplant cohorts.

Infections At the time of HCT, more than 70% of patients had HPV infections; 31% had NTM infections, and in 79%, "other bacterial, fungal, parasitical, or viral infections" were documented. Due to the lack of data or reporting, the number of those without infections cannot be determined. After successful allogeneic HCT, the incidence of HPV, and mycobacterial and fungal infections decreased considerably. Post-transplant infections were reported in approximately 22% of patients, but pathogens appeared to be similar to typical to post-HCT infections in other cohorts. In contrast, opportunistic infections that manifested prior to transplant did not appear to pose a major problem—most likely because patients were kept on antibiotic prophylaxis. In most case reports, no details on antibiotic prophylaxis were given; however, within the clinical phase 1/2 study described above, patients with fully treated NTM infections (negative cultures, lesions stable, or regressing on imaging studies) prior to HCT were kept on prophylactic azithromycin until the time of transplant and about a year after. Patients that were, at the time of transplant, because of recent episodes of infection or bone involvement still under additional rifamycin treatment were switched to moxifloxacin before the start of the conditioning regimen to avoid possible drug interactions. Most patients that were still treated for active infection at the time of transplant were kept on all the anti-mycobacterial drugs at last 6–12 months after transplant [15, 16]. Of note, full immune reconstitution of B, NK, and monocyte populations with reversal of the phenotype and inflammatory lesions can take months to years, in some cases more than 3.5 years, and can be accompanied by immune reconstitution inflammatory syndrome [16, 32] (Supplemental Table 1).

Lungs Pulmonary alveolar proteinosis (PAP) was present in seven reported patients (9% of those with documented symptoms). In four out of seven patients with PAP, a positive family was present; in two out of seven, the family history was negative for immunodeficiencies or myeloid neoplasms. In one out of seven patients, no information is given. Of note, it appears that pulmonary symptoms and function can markedly improve with allogeneic HCT in patients with PAP. The rational for the improvement is via reconstitution of the alveolar macrophage compartment as some of the pulmonary changes seen in *GATA2* deficiency likely result from pulmonary alveolar macrophage dysfunction. One patient with severe pulmonary hypertension and PAP, which made him a lung transplant candidate prior to HCT, responded well but subsequently developed bronchiolitis obliterans and required lung transplantation 4.5 years post-HCT. Another patient died early after transplant. Both patients had severe PAP requiring pulmonary lavage prior to transplant and supplemental oxygen at the time of HCT [15, 16]. As both PAP and pulmonary arterial hypertension respond well to HCT, recurrent lung infections or declining lung function should be considered an indication for allogeneic HCT before severe organ dysfunction manifests (Fig. 4) [32].

Immune reconstitution inflammatory syndrome post-allo-HCT As the immune system regains its potency after prolonged periods of significant immunosuppression, clearance of infectious foci can lead to a paradoxical clinical deterioration when intense inflammatory infiltrates are formed. The so-called IRIS is frequently observed in patients with HIV once highly active antiretroviral therapy (HAART) is initiated and the immune system recovers. Infections associated with IRIS include *Mycobacteria*, *Cryptococci*, CMV, JC virus, and candida. In non-HIV settings, IRIS is a rare phenomenon that has been described mostly in case reports of transplant recipients [40, 41]. Most reported patients were recipients of solid organs, whereas IRIS following allogeneic HCT appears to be less frequent, possibly because of the prolonged immunosuppression used post-HCT [42–45]. Features of IRIS are variable, but onset is usually acute with localized or generalized

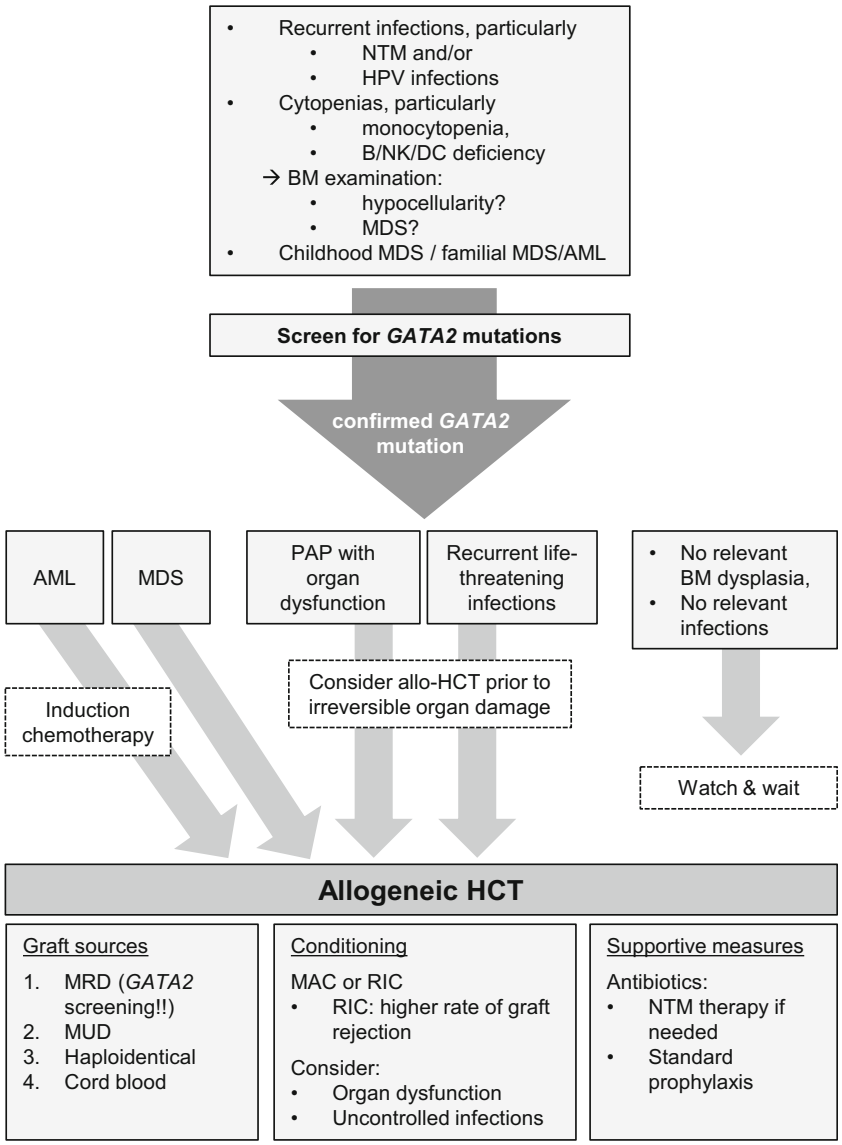


Fig. 4 Diagnostic work-up and therapeutic strategies. No formal recommendations on the indication for allo-HCT, conditioning regimens, donor source, and antibiotic prophylaxis are currently available. NTM non-tuberculous mycobacteria, HPV human papilloma virus, NK natural killer, DC dendritic cell, BM bone marrow, MDS myelodysplastic syndrome, AML acute myeloid leukemia, PAP pulmonary alveolar proteinosis, allo-HCT allogeneic hematopoietic cell transplantation, MRD matched-related donor, MUD matched-unrelated donor. MAC myeloablative conditioning, RIC reduced intensity conditioning

inflammation [45]. Overall, post-transplant IRIS remains a poorly studied entity, and because of the lack of reliable measures to diagnose IRIS in the clinical context, it can be difficult to separate IRIS from worsening of the underlying infectious disease. Thus, it is important to understand these inflammatory syndromes and adjust therapy accordingly—particularly in contexts where patients with prior, long-term immunodeficiencies and chronic opportunistic infections undergoing allogeneic HCT [40, 41].

Discussion

Heterozygous *GATA2* germline mutations can be inherited or acquired de novo. Such *GATA2* deficiency can cause a multifaceted clinical syndrome that typically involves functional and numeric deficiencies of the lymphoid, immune, and hematopoietic systems, often paired with features such as lymphedema, congenital deafness, and, as a consequence of immune dysfunction, opportunistic infections. Most importantly, however, *GATA2* deficiency predisposes patients to the development of malignant hematologic diseases, particularly MDS/AML. The natural history of *GATA2* deficiency is variable, with some patients presenting early in life, often with rather unspecific symptoms, such as recurrent infections, and others becoming symptomatic only after many decades [12].

The human *GATA2* gene is located on chromosome 3q21, has six exons, and belongs to a family of zinc finger transcription factors that are critical regulators in hematopoiesis [46]. *GATA2* transcription is regulated by several transcription factors such as *ETS1*, *BMP4*, *NOTCH1*, *PU.1*, and *EVI1* and by the cytokines IL-1 and TNFα. The dynamic expression patterns of *GATA1* and *GATA2* are critically influencing the coordination of hematopoietic homeostasis, including genesis,

survival, and maintenance of hematopoietic stem cells (HSC) and progenitor cells [47], whereas downregulation of *GATA2* appears to be necessary for lineage differentiation [46]. Accordingly, *GATA2* knockout mice have profound defects in definitive hematopoiesis, and *GATA2* deficient embryos die of anemia at day 10–11 of gestation. In heterozygous adult mice with *GATA2* haploinsufficiency, an increased proportion of quiescent HSC with increased apoptosis can be observed, resulting in defects in the self-renewal and proliferation capacity of HSC, abnormal HSC homeostasis, and a reduced HSC pool [6, 46, 48, 49]. Of note, in humans with myeloid malignancies with inv(3)(q21q26.2) or t(3;3)(q21;q26,2), these chromosomal rearrangements can result in dysregulation of the proto-oncogene *EVI1* at 3q26.2 by reposition of a distal *GATA2* enhancer and thereby ectopically activate *EVI 1*, while simultaneously conferring functional *GATA2* haploinsufficiency [50].

Genetic aberrations of *GATA2* are highly heterogeneous and occur throughout the coding region, resulting in the creation of stop codons, frameshift mutations, deletions, substitutions, indel mutations, and point mutations [12, 34, 47, 51]. To this point, no correlation between the type of *GATA2* mutation and the clinical phenotype could be established [12]. Likewise, the molecular basis for the progression of *GATA2* deficiency into MDS/AML has not been clarified. It is believed that secondary genetic events may be responsible for the clinical heterogeneity among cases with *GATA2* deficiency as well as the progression into MDS/AML, as suggested by a recently published case report: whole genome sequencing in a patient with germline *GATA2* mutation revealed new mutations in *EZH2*, *HECW2*, and *GATA1* that appeared to be important secondary events leading to the development of MDS/AML in this patient [25]. The hypothesis that additional genetic events determine the clinical outcomes, including the development of malignancy, is supported by the fact that *GATA2* deficiency is commonly associated with cytogenetic aberrations, including partial deletion or monosomy of chromosome 7, and additional acquired mutations, such as those in *ASXL1* [10].

Given the genetic heterogeneity and variability of the natural history and course of *GATA2* deficiency, the best timing of allogeneic HCT is not clear. Some carriers remain rather asymptomatic throughout life; however, once symptoms develop, survival declines [1]. Thus, the ideal time for transplant would be after the onset of pathological abnormalities but before the development of organ damage or malignancy (Fig. 4). Practically, this means that with progressive bone marrow dysplasia and occurrence of cytogenetic abnormalities, the primary indication for allogeneic HCT is given. Performing the transplant procedure during the hypocellular phase of MDS allows upfront transplantation, whereas with transformation into overt AML, typically an induction chemotherapy prior to HCT with additional toxicity is necessary. Another indication for transplantation, and thereby replacement of the dysfunctional immune system, is the development of recurrent severe opportunistic infections that can also be life-threatening. Progressive lung injury from infection and PAP represents a third reason for all HCT. Both frequent pneumonias and PAP result in gradual deterioration of lung function, and therefore, HCT should be performed prior to irreversible organ damage [32].

Details of HCT for treatment of *GATA2* deficiencies have not been studied extensively in a prospective fashion. Only two small prospective studies have been performed, one as a pilot study on the feasibility of nonmyeloablative conditioning for allo-HCT ($n = 14$ patients) and one as a follow-up trial testing a more intensive, busulfan-containing regimen ($n = 22$ patients). In addition, there are two larger datasets and a number of case reports and small case series available. Here, we performed a comprehensive search of the available literature on the use of allogeneic HCT in patients with *GATA2* deficiency. In the earlier years, patient preparation was typically done by reduced intensity conditioning due to concerns regarding uncontrolled infections and increased toxicity in these often fragile patients. However, with such reduced intensity conditioning, engraftment failure was observed in a substantial proportion of patients. Thus, in later experiences, more intensive, myeloablative conditioning was used, and this resulted in more uniform engraftment and a reduced risk of relapse [12, 16]. Although available data from those case reports and series do not provide extensive details on post-HCT course and complications, it appears that infections that were recorded were similar to those observed in "normal" transplant cohorts, whereas uncontrolled opportunistic infections during pharmacological immunosuppression were not reported. Likewise, the rate of GVHD appears to be comparable to other cohorts (Table 1 and Supplemental Table 1).

Our case presented here adds to the literature the finding of immune reconstitution inflammatory syndrome (IRIS) in a young woman with *GATA2* deficiency, evolving MDS-MLD and multiple *Mycobacterium abscessus* granulomata. With the reduction of pharmacological immunosuppression, inflammation of the lesions increased and lesions became painful. PET-CT imaging revealed increased metabolic activity. Fearing for uncontrolled infection, a biopsy of the lesion was taken and revealed no evidence of mycobacteria by PCR and culture, which supported the diagnosis of immune reconstitution rather than uncontrolled infection. Ultimately, healing of the granulomatous lesions and the multiple warts on hands and feet took approximately 6–9 months. This case illustrates the typical course and problems encountered during treatment of patients with *GATA2* deficiencies and other states of immune dysfunction and thereby may help to guide treatment decisions of other patients.

Today, it is clear that only allogeneic HCT can cure the dysfunctional hematopoietic and immune systems in patients with *GATA2* deficiency. In the light of evolving gene-repair technologies implementing CRISPR/CAS methodologies, it

appears conceivable that one day, gene therapy represents an alternative treatment approach. Not only would such a repair rectify the incompetence of the immune system, but might also give HSCs an advantage to outcompete cytogenetically abnormal cells and thereby prevent or lower the risk of malignant transformation.

Acknowledgements We are grateful to the patient, whose case is presented here for her willingness to share her medical history and images for publication.

Funding information A.S. is supported by a research fellowship of the Hanne Liebermann Foundation. A.M. is supported by the Promedica Foundation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Spinner MA, Sanchez LA, Hsu AP, Shaw PA, Zerbe CS, Calvo KR, Arthur DC, Gu W, Gould CM, Brewer CC, Cowen EW, Freeman AF, Olivier KN, Uzel G, Zelazny AM, Daub JR, Spalding CD, Claypool RJ, Giri NK, Alter BP, Mace EM, Orange JS, Cuellar-Rodriguez J, Hickstein DD, Holland SM (2014) GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood 123(6):809–821. https://doi.org/10.1182/blood-2013-07-515528
2. Maciejewski-Duval A, Meuris F, Bignon A, Aknin ML, Balabanian K, Faivre L, Pasquet M, Barlogis V, Fieschi C, Bellanne-Chantelot C, Donadieu J, Schlecht-Louf G, Marin-Esteban V, Bachelerie F (2016) Altered chemotactic response to CXCL12 in patients carrying GATA2 mutations. J Leukoc Biol 99(6):1065–1076. https://doi.org/10.1189/jlb.5MA0815-388R
3. Vinh DC, Patel SY, Uzel G, Anderson VL, Freeman AF, Olivier KN, Spalding C, Hughes S, Pittaluga S, Raffeld M, Sorbara LR, Elloumi HZ, Kuhns DB, Turner ML, Cowen EW, Fink D, Long-Priel D, Hsu AP, Ding L, Paulson ML, Whitney AR, Sampaio EP, Frucht DM, DeLeo FR, Holland SM (2010) Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. Blood 115(8):1519–1529. https://doi.org/10.1182/blood-2009-03-208629
4. Calvo KR, Vinh DC, Maric I, Wang W, Noel P, Stetler-Stevenson M, Arthur DC, Raffeld M, Dutra A, Pak E, Myung K, Hsu AP, Hickstein DD, Pittaluga S, Holland SM (2011) Myelodysplasia in autosomal dominant and sporadic monocytopenia immunodeficiency syndrome: diagnostic features and clinical implications. Haematologica 96(8):1221–1225. https://doi.org/10.3324/haematol.2011.041152
5. Bigley V, Haniffa M, Doulatov S, Wang XN, Dickinson R, McGovern N, Jardine L, Pagan S, Dimmick I, Chua I, Wallis J, Lordan J, Morgan C, Kumararatne DS, Doffinger R, van der Burg M, van Dongen J, Cant A, Dick JE, Hambleton S, Collin M (2011) The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency. J Exp Med 208(2):227–234. https://doi.org/10.1084/jem.20101459
6. Dickinson RE, Griffin H, Bigley V, Reynard LN, Hussain R, Haniffa M, Lakey JH, Rahman T, Wang XN, McGovern N, Pagan S, Cookson S, McDonald D, Chua I, Wallis J, Cant A, Wright M, Keavney B, Chinnery PF, Loughlin J, Hambleton S, Santibanez-Koref M, Collin M (2011) Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. Blood 118(10):2656–2658. https://doi.org/10.1182/blood-2011-06-360313
7. Hsu AP, Sampaio EP, Khan J, Calvo KR, Lemieux JE, Patel SY, Frucht DM, Vinh DC, Auth RD, Freeman AF, Olivier KN, Uzel G, Zerbe CS, Spalding C, Pittaluga S, Raffeld M, Kuhns DB, Ding L, Paulson ML, Marciano BE, Gea-Banacloche JC, Orange JS, Cuellar-Rodriguez J, Hickstein DD, Holland SM (2011) Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. Blood 118(10):2653–2655. https://doi.org/10.1182/blood-2011-05-356352
8. Ostergaard P, Simpson MA, Connell FC, Steward CG, Brice G, Woollard WJ, Dafou D, Kilo T, Smithson S, Lunt P, Murday VA, Hodgson S, Keenan R, Pilz DT, Martinez-Corral I, Makinen T, Mortimer PS, Jeffery S, Trembath RC, Mansour S (2011) Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). Nat Genet 43(10):929–931. https://doi.org/10.1038/ng.923
9. Hahn CN, Chong CE, Carmichael CL, Wilkins EJ, Brautigan PJ, Li XC, Babic M, Lin M, Carmagnac A, Lee YK, Kok CH, Gagliardi L, Friend KL, Ekert PG, Butcher CM, Brown AL, Lewis ID, To LB, Timms AE, Storek J, Moore S, Altree M, Escher R, Bardy PG, Suthers GK, D'Andrea RJ, Horwitz MS, Scott HS (2011) Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat Genet 43(10):1012–1017. https://doi.org/10.1038/ng.913
10. Bodor C, Renneville A, Smith M, Charazac A, Iqbal S, Etancelin P, Cavenagh J, Barnett MJ, Kramarzova K, Krishnan B, Matolcsy A, Preudhomme C, Fitzgibbon J, Owen C (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(6):890–894. https://doi.org/10.3324/haematol.2011.054361
11. Johnson JA, Yu SS, Elist M, Arkfeld D, Panush RS (2015) Rheumatologic manifestations of the "MonoMAC" syndrome. A systematic review. Clin Rheumatol 34(9):1643–1645. https://doi.org/10.1007/s10067-015-2905-2
12. Wlodarski MW, Hirabayashi S, Pastor V, Stary J, Hasle H, Masetti R, Dworzak M, Schmugge M, van den Heuvel-Eibrink M, Ussowicz M, De Moerloose B, Catala A, Smith OP, Sedlacek P, Lankester AC, Zecca M, Bordon V, Matthes-Martin S, Abrahamsson J, Kuhl JS, Sykora KW, Albert MH, Przychodzien B, Maciejewski JP, Schwarz S, Gohring G, Schlegelberger B, Cseh A, Noellke P, Yoshimi A, Locatelli F, Baumann I, Strahm B, Niemeyer CM, MDS E (2016) Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. Blood 127(11):1387–1397; **quiz 1518**. https://doi.org/10.1182/blood-2015-09-669937
13. Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM (2013) MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. Clin Infect Dis 57(5):697–699. https://doi.org/10.1093/cid/cit368
14. Lasbury ME, Tang X, Durant PJ, Lee CH (2003) Effect of transcription factor GATA-2 on phagocytic activity of alveolar macrophages from Pneumocystis carinii-infected hosts. Infect Immun 71(9):4943–4952
15. Cuellar-Rodriguez J, Gea-Banacloche J, Freeman AF, Hsu AP, Zerbe CS, Calvo KR, Wilder J, Kurlander R, Olivier KN, Holland SM, Hickstein DD (2011) Successful allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. Blood 118(13):3715–3720. https://doi.org/10.1182/blood-2011-06-365049

16. Grossman J, Cuellar-Rodriguez J, Gea-Banacloche J, Zerbe C, Calvo K, Hughes T, Hakim F, Cole K, Parta M, Freeman A, Holland SM, Hickstein DD (2014) Nonmyeloablative allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. Biol Blood Marrow Transplant 20(12):1940–1948. https://doi.org/10.1016/j.bbmt.2014.08.004
17. Parta M, Shah NN, Baird K, Rafei H, Calvo KR, Hughes T, Cole K, Kenyon M, Schuver BB, Cuellar-Rodriguez J, Zerbe CS, Holland SM, Hickstein DD (2018) Allogeneic hematopoietic stem cell transplantation for GATA2 deficiency using a busulfan-based regimen. Biol Blood Marrow Transplant. https://doi.org/10.1016/j.bbmt.2018.01.030
18. Berry D, Fekrat S (2017) Central retinal vein occlusion in Gata2 deficiency. Retin Cases Brief Rep. https://doi.org/10.1097/ICB.0000000000000558
19. Burroughs LM, Shimamura A, Talano JA, Domm JA, Baker KK, Delaney C, Frangoul H, Margolis DA, Baker KS, Nemecek ER, Geddis AE, Sandmaier BM, Deeg HJ, Storb R, Woolfrey AE (2017) Allogeneic hematopoietic cell transplantation using treosulfan-based conditioning for treatment of marrow failure disorders. Biol Blood Marrow Transplant 23(10):1669–1677. https://doi.org/10.1016/j.bbmt.2017.06.002
20. Ciullini Mannurita S, Vignoli M, Colarusso G, Tucci F, Veltroni M, Frenos S, Tintori V, Arico M, Bigley V, Collin M, Favre C, Gambineri E (2016) Timely follow-up of a GATA2 deficiency patient allows successful treatment. J Allergy Clin Immunol 138(5):1480–1483 **e1484**. https://doi.org/10.1016/j.jaci.2016.06.004
21. Cohen JI, Dropulic L, Hsu AP, Zerbe CS, Krogmann T, Dowdell K, Hornung RL, Lovell J, Hardy N, Hickstein D, Cowen EW, Calvo KR, Pittaluga S, Holland SM (2016) Association of GATA2 deficiency with severe primary Epstein-Barr virus (EBV) infection and EBV-associated cancers. Clin Infect Dis 63(1):41–47. https://doi.org/10.1093/cid/ciw160
22. Ding LW, Ikezoe T, Tan KT, Mori M, Mayakonda A, Chien W, Lin DC, Jiang YY, Lill M, Yang H, Sun QY, Koeffler HP (2017) Mutational profiling of a MonoMAC syndrome family with GATA2 deficiency. Leukemia 31(1):244–245. https://doi.org/10.1038/leu.2016.256
23. Fisher KE, Hsu AP, Williams CL, Sayeed H, Merritt BY, Elghetany MT, Holland SM, Bertuch AA, Gramatges MM (2017) Somatic mutations in children with GATA2-associated myelodysplastic syndrome who lack other features of GATA2 deficiency. Blood Adv 1(7):443–448. https://doi.org/10.1182/bloodadvances.2016002311
24. Fox TA, Chakraverty R, Burns S, Carpenter B, Thomson K, Lowe D, Fielding A, Peggs K, Kottaridis P, Uttenthal B, Bigley V, Buckland M, Grandage V, Denovan S, Grace S, Dahlstrom J, Workman S, Symes A, Mackinnon S, Hough R, Morris E (2018) Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. Blood 131(8):917–931. https://doi.org/10.1182/blood-2017-09-807487
25. Fujiwara T, Fukuhara N, Funayama R, Nariai N, Kamata M, Nagashima T, Kojima K, Onishi Y, Sasahara Y, Ishizawa K, Nagasaki M, Nakayama K, Harigae H (2014) Identification of acquired mutations by whole-genome sequencing in GATA-2 deficiency evolving into myelodysplasia and acute leukemia. Ann Hematol 93(9):1515–1522. https://doi.org/10.1007/s00277-014-2090-4
26. Koegel AK, Hofmann I, Moffitt K, Degar B, Duncan C, Tubman VN (2016) Acute lymphoblastic leukemia in a patient with MonoMAC syndrome/GATA2 haploinsufficiency. Pediatr Blood Cancer 63(10):1844–1847. https://doi.org/10.1002/pbc.26084
27. Lovell JP, Zerbe CS, Olivier KN, Claypool RJ, Frein C, Anderson VL, Freeman AF, Holland SM (2016) Mediastinal and disseminated Mycobacterium kansasii disease in GATA2 deficiency. Ann Am Thorac Soc 13(12):2169–2173. https://doi.org/10.1513/AnnalsATS.201603-207BC
28. Lubking A, Vosberg S, Konstandin NP, Dufour A, Graf A, Krebs S, Blum H, Weber A, Lenhoff S, Ehinger M, Spiekermann K, Greif PA, Cammenga J (2015) Young woman with mild bone marrow dysplasia, GATA2 and ASXL1 mutation treated with allogeneic hematopoietic stem cell transplantation. Leuk Res Rep 4(2):72–75. https://doi.org/10.1016/j.lrr.2015.10.001
29. Maeurer M, Magalhaes I, Andersson J, Ljungman P, Sandholm E, Uhlin M, Mattsson J, Ringden O (2014) Allogeneic hematopoietic cell transplantation for GATA2 deficiency in a patient with disseminated human papillomavirus disease. Transplantation 98(12):e95–e96. https://doi.org/10.1097/TP.0000000000000520
30. Mallhi K, Dix DB, Niederhoffer KY, Armstrong L, Rozmus J (2016) Successful umbilical cord blood hematopoietic stem cell transplantation in pediatric patients with MDS/AML associated with underlying GATA2 mutations: two case reports and review of literature. Pediatr Transplant 20(7):1004–1007. https://doi.org/10.1111/petr.12764
31. Mansour S, Connell F, Steward C, Ostergaard P, Brice G, Smithson S, Lunt P, Jeffery S, Dokal I, Vulliamy T, Gibson B, Hodgson S, Cottrell S, Kiely L, Tinworth L, Kalidas K, Mufti G, Cornish J, Keenan R, Mortimer P, Murday V, Lymphoedema Research C (2010) Emberger syndrome-primary lymphedema with myelodysplasia: report of seven new cases. Am J Med Genet A 152A(9):2287–2296. https://doi.org/10.1002/ajmg.a.33445
32. Mir MA, Kochuparambil ST, Abraham RS, Rodriguez V, Howard M, Hsu AP, Jackson AE, Holland SM, Patnaik MM (2015) Spectrum of myeloid neoplasms and immune deficiency associated with germline GATA2 mutations. Cancer Med 4(4):490–499. https://doi.org/10.1002/cam4.384
33. Parta M, Cuellar-Rodriguez J, Freeman AF, Gea-Banacloche J, Holland SM, Hickstein DD (2017) Resolution of multifocal Epstein-Barr virus-related smooth muscle tumor in a patient with GATA2 deficiency following hematopoietic stem cell transplantation. J Clin Immunol 37(1):61–66. https://doi.org/10.1007/s10875-016-0360-8
34. Pasquet M, Bellanne-Chantelot C, Tavitian S, Prade N, Beaupain B, Larochelle O, Petit A, Rohrlich P, Ferrand C, Van Den Neste E, Poirel HA, Lamy T, Ouachee-Chardin M, Mansat-De Mas V, Corre J, Recher C, Plat G, Bachelerie F, Donadieu J, Delabesse E (2013) High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia. Blood 121(5):822–829. https://doi.org/10.1182/blood-2012-08-447367
35. Polat A, Dinulescu M, Fraitag S, Nimubona S, Toutain F, Jouneau S, Poullot E, Droitcourt C, Dupuy A (2017) Skin manifestations among GATA2-deficient patients. Br J Dermatol 178:781–785. https://doi.org/10.1111/bjd.15548
36. Ramzan M, Lowry J, Courtney S, Krueger J, Schechter Finkelstein T, Ali M (2017) Successful myeloablative matched unrelated donor hematopoietic stem cell transplantation in a young girl with GATA2 deficiency and Emberger syndrome. J Pediatr Hematol Oncol 39(3):230–232. https://doi.org/10.1097/MPH.0000000000000737
37. Rastogi N, Abraham RS, Chadha R, Thakkar D, Kohli S, Nivargi S, Prakash Yadav S (2017) Successful nonmyeloablative allogeneic stem cell transplant in a child with Emberger syndrome and GATA2 mutation. J Pediatr Hematol Oncol. https://doi.org/10.1097/MPH.0000000000000995
38. Saida S, Umeda K, Yasumi T, Matsumoto A, Kato I, Hiramatsu H, Ohara O, Heike T, Adachi S (2016) Successful reduced-intensity stem cell transplantation for GATA2 deficiency before progression of advanced MDS. Pediatr Transplant 20(2):333–336. https://doi.org/10.1111/petr.12667
39. Shah NN, Parta M, Baird K, Rafei H, Cole K, Holland SM, Hickstein DD (2017) Monozygotic twins with GATA2 deficiency: same haploidentical-related donor, different severity of GvHD.

Bone Marrow Transplant 52(11):1580–1582. https://doi.org/10.1038/bmt.2017.180

40. Sun HY, Singh N (2009) Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis 22(4):394–402. https://doi.org/10.1097/QCO.0b013e32832d7aff
41. Sun HY, Singh N (2011) Opportunistic infection-associated immune reconstitution syndrome in transplant recipients. Clin Infect Dis 53(2):168–176. https://doi.org/10.1093/cid/cir276
42. Airas L, Paivarinta M, Roytta M, Karhu J, Kauppila M, Itala-Remes M, Remes K (2010) Central nervous system immune reconstitution inflammatory syndrome (IRIS) after hematopoietic SCT. Bone Marrow Transplant 45(3):593–596. https://doi.org/10.1038/bmt.2009.186
43. Sinha A, Abinun M, Gennery AR, Barge D, Slatter M, Cheetham T (2013) Graves' immune reconstitution inflammatory syndrome in childhood. Thyroid 23(8):1010–1014. https://doi.org/10.1089/thy.2012.0618
44. Lopez-Iniguez A, Carrera-Villanueva KA, Leon-Rodriguez E, Cuellar-Rodriguez J (2017) Recurrent arthritis and immune reconstitution inflammatory syndrome in hematopoietic stem cell transplantation (HSCT). Bone Marrow Transplant 53:374–376. https://doi.org/10.1038/s41409-017-0058-4
45. Shah RM, Waugh S, Ng KF, Gennery AR, Slatter M, Cant AJ (2017) Enterovirus-related immune reconstitution inflammatory syndrome (IRIS) following haploidentical stem cell transplantation in an MHC class II-deficient child. J Clin Immunol 37(5):419–421. https://doi.org/10.1007/s10875-017-0402-x
46. Vicente C, Conchillo A, Garcia-Sanchez MA, Odero MD (2012) The role of the GATA2 transcription factor in normal and malignant hematopoiesis. Crit Rev Oncol Hematol 82(1):1–17. https://doi.org/10.1016/j.critrevonc.2011.04.007
47. Shimizu R, Yamamoto M (2016) GATA-related hematologic disorders. Exp Hematol 44(8):696–705. https://doi.org/10.1016/j.exphem.2016.05.010
48. de Pater E, Kaimakis P, Vink CS, Yokomizo T, Yamada-Inagawa T, van der Linden R, Kartalaei PS, Camper SA, Speck N, Dzierzak E (2013) Gata2 is required for HSC generation and survival. J Exp Med 210(13):2843–2850. https://doi.org/10.1084/jem.20130751
49. Rodrigues NP, Boyd AS, Fugazza C, May GE, Guo Y, Tipping AJ, Scadden DT, Vyas P, Enver T (2008) GATA-2 regulates granulocyte-macrophage progenitor cell function. Blood 112(13):4862–4873. https://doi.org/10.1182/blood-2008-01-136564
50. Groschel S, Sanders MA, Hoogenboezem R, de Wit E, Bouwman BAM, Erpelinck C, van der Velden VHJ, Havermans M, Avellino R, van Lom K, Rombouts EJ, van Duin M, Dohner K, Beverloo HB, Bradner JE, Dohner H, Lowenberg B, Valk PJM, Bindels EMJ, de Laat W, Delwel R (2014) A single oncogenic enhancer rearrangement causes concomitant EVI1 and GATA2 deregulation in leukemia. Cell 157(2):369–381. https://doi.org/10.1016/j.cell.2014.02.019
51. Collin M, Dickinson R, Bigley V (2015) Haematopoietic and immune defects associated with GATA2 mutation. Br J Haematol 169(2):173–187. https://doi.org/10.1111/bjh.13317