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RESEARCH

Bone Marrow CD8 + Abundance Inversely Correlates with Progressive Marrow Fibrosis and Myelodysplastic Evolution in GATA2 Deficiency: Case Report

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Abstract

Purpose GATA2 deficiency, a rare inborn error of immunity, presents with highly variable phenotypes. Bone marrow (BM) changes such as hypocellularity and myelodysplastic syndrome (MDS) are common, with hematopoietic stem cell transplantation being the only curative option due to the risk of progression to acute myeloid leukemia. Although traditional markers like cytogenetic abnormalities and somatic mutations (e.g., *ASXL1*) identify the risk of leukemic transformation, efforts to identify novel predictors of disease evolution are needed. CD8+ T cells are known to play a key role in MDS immune surveillance, but their specific involvement in GATA2 deficiency remains poorly defined.

Methods In this case report, we report on a young adult with GATA2 deficiency who underwent longitudinal monitoring of both peripheral and BM lymphocyte subsets, with a focus on CD8+ T-cell evolution in relation to MDS progression.

Results The patient exhibited typical GATA2-deficient immune-hematological findings, including monocytopenia, B- and NK-cell deficiency, but had no history of severe infections and remained transfusion-independent. While peripheral CD8+ T-cell levels remained stable over time, a notable reduction in BM CD8+ T cells was observed in association with MDS progression.

Conclusion Providing a long-term follow-up of one GATA2-deficient patient, we suggest that a decrease in BM CD8+ T cells may serve as an early marker of immune surveillance escape and disease progression. These findings underscore the need for further investigation into the role of BM CD8+ T cells in GATA2 deficiency and MDS evolution, potentially offering new insights for follow-up and therapeutic intervention.

Keywords GATA2 deficiency · Myelofibrosis · Myelodysplastic syndrome · T Lymphocytes

Introduction

GATA2 deficiency is a rare autosomal genetic disease due to heterozygous germline variants (familial or *de novo*) in the *GATA2* gene. The *GATA2* gene encodes a transcription factor that plays a critical role in the hematopoiesis. The clinical phenotype is wide and variable, encompassing, from the hematological point of view, cytopenia and bone marrow (BM) hypocellularity as well as myelodysplastic syndrome (MDS) and myeloid neoplasms [1, 2]. Evidence suggests that T-cell immune system contributes to the pathogenesis, maintenance, and progression of MDS, as reviewed by Rodriguez-Sevilla et al. [3] Although T-cell exhaustion has been reported [4], BM T-cell investigations, including

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CD8+ abundance, have not been investigated in GATA2 deficiency.

Here, we describe the long-term follow up of one previously described GATA2 deficient patient [1, 5, 6] who developed MDS, progressive triple-negative marrow fibrosis (MF) and an additional somatic *ASXL1* variant, detailing the kinetics of peripheral and BM lymphocytes over time.

Methods

Informed Consent

Patient and parents gave informed consent to be part of the study, approved by Brianza ethical committee (GATA2.IT) and conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and with the Declaration of Helsinki.

Myeloid Panel Sequencing Analysis

In patient's BM samples, next generation sequencing (NGS) analysis was performed using SOPHiA GENETICS™ Myeloid Solution, a captured based system used to address somatic variants in 30 genes associated with myelodysplastic syndromes, myeloproliferative neoplasms, and leukemia. Libraries prepared according to manufacturer instructions were sequenced following the Illumina protocol paired-end 2x250bp. Analysis of Fastq files was performed with The SOPHiA DDM™ platform and only variants with a minimum coverage of 1000X were taken into account and analyzed for their possible pathogenicity.

Next-Generation Sequencing of T-Cell Receptor Gene Recombinations

Amplicon-based NGS of T-cell receptor (TR) gene rearrangements for clonality assessment was performed as previously described, according to EuroClonality procedures [7].

Pathology

The BM biopsy samples of the patient were retrieved from the Digital Pathology archives of the Pathology Department, Fondazione IRCCS San Gerardo dei Tintori, University of Milano-Bicocca, Monza, Italy, along with the original reports for pathology review. Histological characteristics (marrow cellularity, reticulin increase and myelofibrosis, megakaryocytes, myeloid and erythroid cells characteristics) were reported. For immunohistochemistry (IHC), 3 µm FFPE sections from the cases were deparaffinized and rehydrated. After endogenous peroxidase blockage and antigen retrieval the slides were incubated with the primary antibodies anti-CD3 (clone 2GV6, Ventana Roche, Tucson, USA) and CD8 (clone SP239, Ventana Roche), all prediluted, in the Ventana Benchmark platform (Roche).

Digital Pathology Pipeline

Slides from Hematoxylin and Eosin (H&E) and IHC for all the cases were scanned using the MIDI II scanner (3DHISTECH, Budapest, Hungary). The obtained whole slide images (WSI) have been imported in the QuPath v0.5.1 software for the computational analysis [8]. The quantification of absolute and relative number of CD3+ and CD8+ cells was performed using the StarDist cell detection extension [9] coupled with an object classifier within the QuPath software, as previously described [10]. Absolute number of cells of the whole biopsy and of those positive for the tested markers were extracted in a Google Spreadsheet (Google, Mountain View, CA, USA) and subsequent percentages and ratios were calculated.

Results

A 16-year-old female patient was referred due to persistent leuko-neutropenia, first identified following a single episode of gastrointestinal infection (cultures not performed). Her medical history was unremarkable for recurrent or severe infections, including bacterial, atypical mycobacterial, fungal, or viral etiologies. She suffered from recurrent oral aphthosis, underwent surgical correction of sacrococcygeal fistula and was undergoing periodical gynecological follow-up due to left ovarian cysts. No organomegaly was found at physical examination. Laboratory investigations, including a complete blood count (CBC) with differential and lymphocyte subset analysis, confirmed leuko-neutropenia and showed monocytopenia, thrombocytopenia, and both B- and NK-cell deficiency. Morphological evaluation of BM and trephine biopsy were consistent with refractory cytopenia of childhood (RCC; mononucleated/hypolobulated megakaryocytes and micromegakaryocytes and erythroid dysplasia) [11]. Fibrosis was not detected and cellularity was mildly decreased (40%). The karyotype was normal and one germline *de novo GATA2*mutation was detected (c.380_383dupACCC;p.(Ser129Profs*57)).

As the girl was not transfusion dependent and the neutropenia was mild-to-moderate without severe or frequent infections, close monitoring was initiated with annual BM biopsy and aspiration and twice-yearly CBC. CBC with differential and cytogenetic analysis, including FISH to assess for monosomy 7, did not reveal any abnormalities or changes over the years. A progressive decrease in BM cellularity was observed (40% to 5-10%; biopsy #1 to #5), with a consensual increase in reticulin fibers (MF0 to 2), and a progressive

reduction of hematopoietic cellularity. Megakaryocytes progressively reduced, being virtually absent towards the last two biopsies. The same was reported for myeloid and erythroid cells, experiencing a suppression over time, with a relative increase in immature/precursor forms, until only rare isolated hemopoietic islands were noted in the last biopsies (Table 1 and Figure 1A). There was no significant increase in CD34-positive immature cells over time in BM biopsies, with values remaining almost consistently around 1% of the overall BM cellularity. At the age of 23 (biopsy #4), targeted sequencing analysis of genes frequently mutated in myeloid neoplasms revealed the somatic *ASXL1*mutation (c.1934dupG:p.(Gly646Trpfs*12) with a variant allele frequency (VAF) of 10.8%. No variants in *JAK2*,*CALR* or*MPL* were detected. One year later, *ASXL1*VAF increased up to 15% with wild type status of *JAK2*,*CALR* or*MPL*.

Large granular lymphocytes (LGL) were retrospectively detected in the first three BM smears, being absent in the last two. T-cell clonality was assessed using NGS of TR gene rearrangements, which revealed no clonal or oligoclonal rearrangements. Using a computational pipeline to quantify the absolute number of CD3+ and CD8+ T lymphocytes within the BM biopsies, a relative abundance of the cytotoxic profile was noted, corresponding to almost the totality of T lymphocytes in the first three biopsies. The decrease of the cytotoxic elements in the last two biopsies led to a progressive reduction of the BM CD8/CD3 ratio, without an overt correlation with peripheral blood (PB) T cells. PB CD3+, CD4+ and CD8+ remained stable over time with inverted CD4:CD8 ratio and, at the time of biopsy #5, PB T-cell subsets showed, either in CD4+ or CD8+, a predominant TEMRA (effector memory cells re-expressing CD45RA) phenotype (CD4+ TEMRA 23.7%, normal value 0.3-9.1%; CD8+ TEMRA 80.1%, normal value 5.2-63.5%) and an increased proportion of atypical CD8+CD56+ population (29%; Table 1, Table 2 and Figure 1A). At the time of the last follow-up visit, when the patient was 24 years old, she remained in good clinical condition, transfusion independent and with no cytogenetic abnormalities. Thereafter the patient transitioned to adult care.

Discussion

Germline *GATA2* mutations are one of the most frequent constitutional defects predisposing to pediatric MDS [2]. Compared with adult MDS, GATA2-associated MDS usually presents with hypocellular BM. Second hits, such as cytogenetic changes or somatic mutations, are frequently associated with increased proliferation, resulting in changes in BM cellularity [12]. The timing for HSCT in GATA2-deficient patients without risk factors (such as cytogenetic abnormalities, severe cytopenia, severe/recurrent infections or advanced disease) is debated. Our patient, lacking such risk factors, was managed conservatively, but recent evidence highlights that somatic mutations, like *ASXL1*, which can be present in 20% of GATA2 patients [13, 14], can worsen outcomes [13].

Fibrosis can be detected in 10–20% of adult MDS [15] cases and up to 73% of GATA2-deficient patients [16, 17], either at initial diagnosis or during the follow-up. In MDS patients, fibrosis predicts poorer overall survival along with higher rate of leukemic transformation [15]. However, GATA2-associated MDS is now recognized as a a distinct disease entity by the International Consensus Classification (ICC) and WHO classification of myeloid neoplasms [18]. Unlike primary myelofibrosis (PMF), a myeloproliferative neoplasm characterized by stem-cell clonal myeloproliferation and driver mutations in *JAK2*, *MPL* or *CALR* genes [19], such mutations have not been described in large GATA2 cohorts [13, 14]. Only one case of germline *GATA2* with somatic *JAK2* mutation has been reported [20]. In contrast, mutations in *ASXL1* and *STAG2* are more commonly observed in GATA2-associated MDS, consistent with its unique pathogenesis. Our patient did not exhibit additional molecular features commonly seen in PMF, and *ASXL1* mutations, while present in up to one-third of PMF patients, are less frequent in triple-negative (wild type *JAK2*, *CALR* or *MPL*) individuals [19].

How fibrosis in GATA2-deficient patients relates to immune dysfunction remains unclear. Although in PMF percentages of CD4, CD8 and their subsets have been shown to be similar either in PB or BM [21], decreasing CD8+ T-cell counts in BM are associated with progression from low-risk to high-risk MDS [3]. Here we describe that inverted PB CD4:CD8 ratio, T-cell counts and subsets remained stable during follow-up with expansion of CD4 and CD8 TEMRA and reduction of BM CD8+. Thus, in GATA2 deficiency, BM CD8+ seems to follow the MDS progression rather than PMF evolution, possibly reflecting immune surveillance escape and impaired anti-tumor activity.

T-cell exhaustion and functional impairment of cytotoxic T-cell, inverted CD4:CD8 ratio and restricted and activated T-cell repertoire have been related to tumor microenvironment, age-related changes, chronic viral infections and have been described either in PMF [21] and MDS [3]. Abnormal patterns of T-cell gene rearrangements were reported in the BM of GATA2 individuals [16, 17]. PB or BM flow cytometry showed inverted CD4:CD8 ratio in GATA2 patients [4, 16]. Ruiz-Garcia et al. [4] reported an association between increased PB CD8+ TEMRA and a more severe phenotype in GATA2 patients. However, these findings require further validation due to several limitations. First, increased TEMRA percentages were observed in only two out of four patients. Second, the analysis relied solely on percentages without

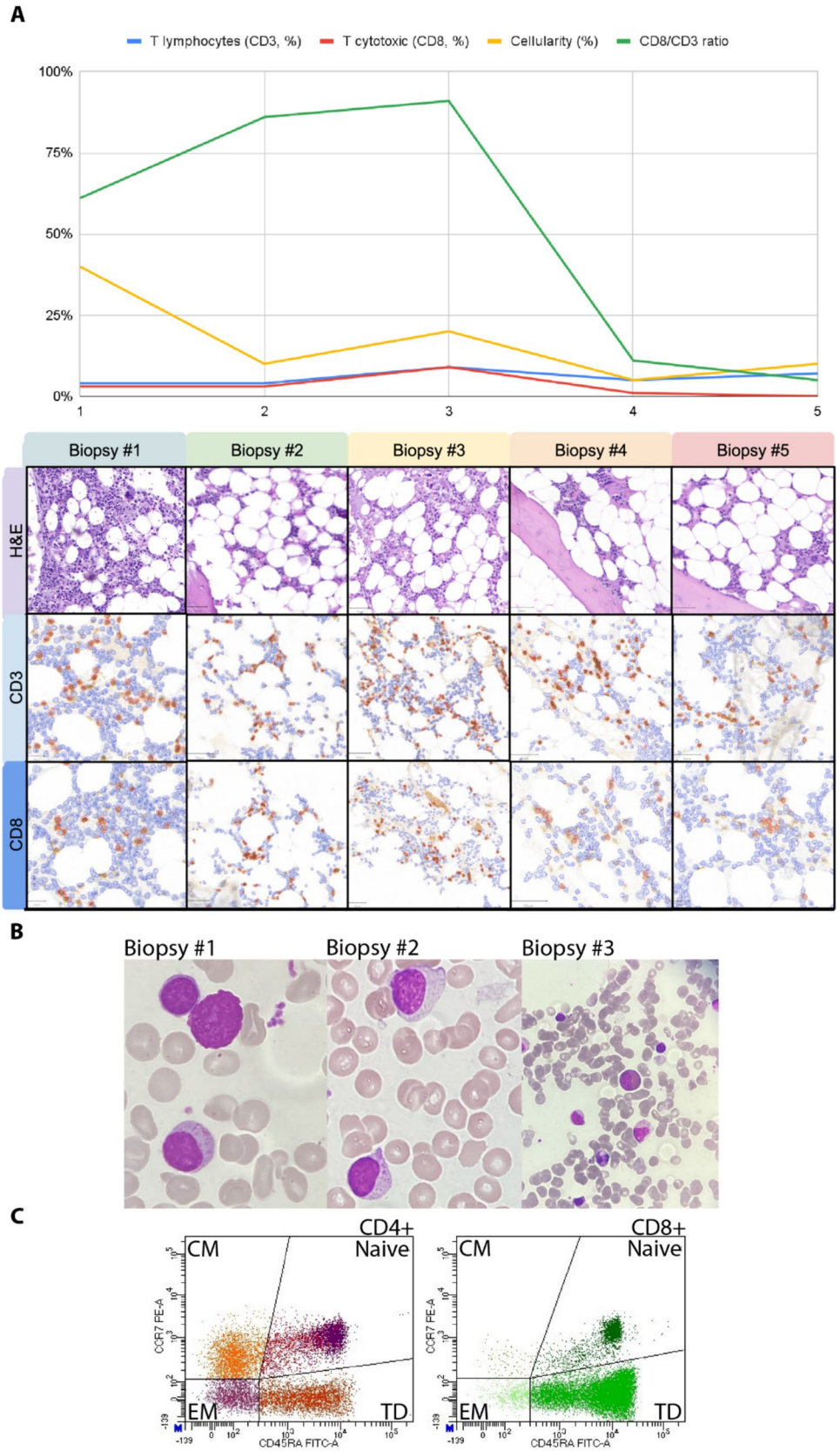

Fig. 1 Comparison of bone marrow modifications during the follow-up and peripheral blood T cell subsets. (**A**) Modification in total marrow cellularity and T lymphocyte count, overall (CD3+) and with cytotoxic profile (CD8+), from the onset to the last biopsy. A progressive decrease in bone marrow cellularity can be appreciated, with concurrent and consensual reduction of both CD3 + and CD8 + T lymphocytes, whose ratio remains almost constant until the last two biopsies. (**B**) Large granular lymphocytes in the first three bone marrow smears. (**C**) Flow cytometric analysis of peripheral blood at the time of biopsy #5 showing increased CD45RA+/CCR7- terminally differerntiated CD4+ (23.7%, normal value 0.3–9.1%; left) and CD8+ (80.1%, normal value 5.2–63.5%; right). CM = central memory. EM = effector memory. TD = terminally differentiated

Table 1 Longitudinal follow-up of peripheral blood lymphocyte subsets and bone marrow features

Age	17	Age-matched normal values (12–18 years)	19	22	23	24	Age-matched normal values (> 18 years)
Peripheral blood							
Complete blood count with differential							
Hemoglobin, g/dl	11.8	12.0–16.0 (female)	11.5	11.8	12	13.1	12.0–16.0 (female)
MCV, fl.	90.6	78–102	91.2	94			80–100
WBC, cells/mm^3	2080	4500–13,000	2610	2560	2890	3200	4500–11,000
Neutrophils, cells/mm^3 (%)	670 (32)	1500–9500 (34–84)	1220 (47)	710 (28)	1530 (53)	2010 (63)	1500–8500 (35–66)
Lymphocytes, cells/mm^3 (%)	1310 (63)	1100–6000 (25–45)	1230 (47)	1760 (69)	1350 (44)	1090 (34)	1100–5000 (20–50)
Monocytes, cells/mm^3 (%)	104 (5)	200–800 (4–10)	130 (5)	50 (2)	50 (2)	60 (2)	200–800 (4–10)
Eosinophils, cells/mm^3 (%)	0	0–500 (0–3)	0	30 (2)	0	30 (1)	0–500 (0–3)
Basophils, cells/mm^3 (%)	0	(0–1)	0	0	0	0	(0–1)
Platelets, cells/mm^3 (%)	109,000	150,000–450,000	118,000	163,000	180,000	170,000	150,000–450,000
Lymphocyte subsets, cells/mm^3 (%)							
CD3+	1141 (87)	740–2731 (58–80)	1066 (87)	896 (51)	1220 (90)	993 (91)	721–2562 (57–88)
CD4+	514 (39)	379–1733 (28–53)	538 (44)	400 (23)	492 (36)	390 (36)	273–1882 (29–66)
CD8+	567 (43)	255–794 (12–32)	484 (39)	448 (26)	615 (46)	507 (47)	177–783 (11–38)
CD4:CD8	0.91		1.11	0.82	0.8	0.77	
CD19+	57 (4)	98–1220 (6–25)	41 (3)	34 (2)	35 (3)	25 (2)	86–648 (6–22)
CD16+CD56+	37 (3)	79–918 (4–25)	32 (3)	22 (1)	59 (4)	39 (4)	40–741 (3–28)
Bone marrow							
Biopsy	#1		#2	#3	#4	#5	
Cellularity	40%		10%	20%	5%	10%	
Marrow fibrosis	0		0	1	2	2	
Megakaryocytes	Mild atypia		Reduced in number, atypical	Reduced in number, atypical	Virtually absent	Virtually absent	
Myeloid cells	Normal		Reduced, increased precursors	Reduced, increased precursors	Suppressed, rare precursors	Rare isolated islands	
Erythroid cells	Dyserythropoiesis		Megaloblastosis	Dyserythropoiesis, hyperplastic loci	Suppressed, rare precursors	Rare isolated islands	
Cytogenetics	Normal		Normal	Normal	Normal	Normal	
Large granular lymphocytes, %/total lymphocytes	27%		13%	15%	0%	0%	
Computational pathology							
Total cells (n)	98,498		46,614	40,172	9459	27,501	
CD3 (n and %)	4335 (4%)		1806 (4%)	3787 (9%)	507 (5%)	1901 (7%)	
CD8 (n and %)	2637 (3%)		1554 (3%)	3450 (9%)	56 (1%)	90 (0%)	

Table 1 (continued)

Age	17	Age-matched normal values (12–18 years)	19	22	23	24	Age-matched normal values (> 18 years)
Peripheral blood							
Complete blood count with differential							
CD8/CD3 ratio	61%		86%	91%	11%	5%	

Numbers in italics indicate values above the normal range, and numbers in boldface indicate values below the normal range for age-matched controls

providing absolute cell counts, which limits interpretability. Finally, these patients, in contrast to our case, had a long history of severe and recurrent infections, which could independently influence CD8+ TEMRA dynamics. Therefore, while these observations are intriguing, additional studies with larger cohorts and comprehensive immunophenotyping are needed to confirm these findings. Dysfunctional CD8+ anti-tumor activity and immune surveillance escape have been linked to the CD8+ exhausted phenotype and impaired metabolic activity. Experimental approaches, such as inhibitory receptors blockade or mitochondrial transfer, have been shown to effectively reverse the CD8+ exhausted phenotype and ultimately enhance the CD8 anti-tumor activity [22, 23]. While these therapies are not intended to address the BM failure or multilineage cytopenia that necessitate HSCT in GATA2 deficiency, the exhausted CD8+ phenotype and the mitochondrial defect observed in GATA2-deficient CD34 + cells [24], suggest that similar mechanism may contribute to immune dysfunction. A deeper understanding of the alterations in GATA2-deficient CD8+ cells could lead to future strategies to restore immune surveillance, complementing standard treatments like HSCT.

The limitations of this study include its retrospective nature and reliance on a single patient, highlighting the need for confirmation in larger, prospective cohorts. Additionally, PB samples were not available, preventing a comparative assessment of the percentage of LGL between the BM and PB. Lastly, LGL phenotyping was not performed, restricting the ability to precisely determine whether the LGL were of T or NK lineage.

Our case shows that, even in young adults and in the absence of chronic viral infections, GATA2 BM microenvironment may recapitulate MDS BM abnormalities and be associated with progressive triple-negative marrow fibrosis. Monitoring of BM CD8+ could be of use in GATA2 deficiency. Further studies regarding BM T-cell phenotype, gene, protein, and metabolic profiles will shed a light into GATA2 BM microenvironment and MDS evolution.

Table 2 Immunological investigations performed at 24 years of age (biopsy #5)

			Age-matched normal values
T lymphocytes, cells/uL	CD3+	993	721–2562
T helper lymphocytes, cells/uL	CD3 + CD4+	390	273–1882
Recent thymic emigrants, cells/uL	CD45RA + CCR7 + CD31+	80	115–913
Naive, %	CD45RA + CCR7+	31.8	20.4–63.6
Central Memory, %	CD45RA-CCR7+	27.5	18.7–46.2
Effector Memory, %	CD45RA-CCR7-	16.9	7.1–38.0
Terminally Differentiated, %	CD45RA + CCR7−	***23.7***	0.3–9.1
T cytotoxic lymphocytes, cells/uL	CD3 + CD8+	507	177–783
Naive, %	CD45RA + CCR7+	16.6	13.1–66.5
Central memory, %	CD45RA-CCR7+	0.6	2.6–24.5
Effector memory, %	CD45RA-CCR7−	2.7	10.1–47.4
Terminally differentiated, %	CD45RA + CCR7−	***80.1***	5.2–63.5
B lymphocytes, cells/uL	CD19+	25	86–648
NK cells, cells/uL	CD3–CD56 + CD16+	39	40–741

Numbers in italics indicate values above the normal range, and numbers in boldface indicate values below the normal range for age-matched controls

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Author Contributions FV wrote the manuscript and interpreted data. VLI analyzed the pathology data. FM performed NGS. OM and SS analyzed bone marrow smears. MC analyzed peripheral immune phenotyping. FS conceived and coordinated the study, interpreted the data and co-wrote the manuscript. FV, SR, VLI, FG, FM, MC, OM, SS, GF, RP, SB, AB and FS discussed the results and commented on the manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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