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BRIEF REPORT

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Severe, persistent, and fatal T-cell immunodeficiency following therapy for infantile leukemia

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Abstract

We describe five cases of children who completed chemotherapy for infantile acute lymphoblastic leukemia (ALL) and soon after were diagnosed with severe T-cell, non-HIV immunodeficiency, with varying B-cell and NK-cell depletion. There was near absence of $CD3^+$, $CD4^+$, and $CD8^+$ cells. All patients developed multiple, primarily opportunistic infections. Unfortunately, four patients died, although one was successfully treated by hematopoietic stem cell transplantation. These immunodeficiencies appeared to be secondary to intensive infant ALL chemotherapy. Our report highlights the importance of the early consideration of this life-threatening immune complication in patients who received chemotherapy for infantile ALL.

KEYWORDS

ALL, death, immunocompromised host, immunodeficiency, infant leukemia, molecular diagnosis and therapy

1 | INTRODUCTION

Intensification of therapy for infants with acute lymphoblastic leukemia (ALL) has resulted in fewer relapses, but at the cost of increased morbidity and death, especially during induction therapy.[1,2] Increased nonhematological toxicity during modern treatment strategies for infant ALL has been reported, but severe immunodeficiency persisting after therapy has not been described.

Immunodeficiencies are classified as acquired or primary (PID). Congenital T-cell immunodeficiencies, defined as $CD3^+$ less than 300 cells/μl,[3] are generally more severe, compared to other immunodeficiencies, since T-cells also play a crucial role in the function of B-cells, NK-cells, and macrophages. Chemotherapy is known to induce an immunodeficiency state by significantly depleting T-cells, as well as NK-cells and B-cells.[4,5] Usually, immune reconstitution begins after completing chemotherapy. In children, greater than 2 years of age, who received intense chemotherapy for treatment of high-risk ALL, T-cell recovery was complete 12–18 months after cessation of chemotherapy. In addition, the absolute $CD3^+$ count at 1 month was greater than 300 cells/μl in these patients.[5,6]

We describe five children who completed treatment for infantile ALL and soon after were diagnosed with persistent severe T-cell, non-HIV, immunodeficiency, with varying B-cell and NK-cell depletion, resulting in severe infections causing death in four and successful hematopoietic stem cell transplantation (HSCT) in one. The immune deficiency appeared to be secondary to their therapy. Our report highlights the importance of considering this complication in patients with infant ALL post chemotherapy.

2 | RESULTS

The IWK Health Centre Research Ethics Board reviewed this manuscript and provided a letter of support. We collected data on five infant cases, four females and one male, treated at three centers in North America between 1996 and 2015. Clinical and treatment characteristics are shown in Table 1. None of the patients received experimental agents or HSCT during initial treatment. All patients completed protocol therapy. Most patients developed infections during treatment despite intravenous immunoglobulins and pneumocystis prophylaxis as per protocol guidelines.

All patients were healthy with no hospital admissions prior to the diagnosis of ALL, except Patient E had a history of urinary tract infections, acute otitis media, and chronic rhinorrhea. These infections did not require hospital admission or intravenous antibiotics. None of the patients had a family history that placed them at risk for PID, except patient B. Her parents were third cousins and from a First Nation's community in which children had previously been diagnosed with severe combined immunodeficiency (SCID), *RAG2* mutation, for which

TABLE 1 Patient information pertaining to leukemia diagnosis and treatment

	Patient A	Patient B	Patient C	Patient D	Patient E
Diagnosis	MLL-R ALL	MLL-R ALL	MLL-R ALL	MLL nonrearranged ALL	MLL nonrearranged ALL
Age at diagnosis	5 month old	5 month old	7 month old	8 month old	11 month old
Treatment	COG AALL0631[a]	COG AALL0631[b]	COG AALL0631[b]	CCG 1953	CCG P9407
	No Lestaurtanib	No Lestaurtanib	No Lestaurtanib		
Treatment course complications	Bacterial and fungal infections	Bacterial and viral infections, extensive thrombi involving upper venous system, enteritis	None	Bacterial and viral infections	Bacterial infections, chronic rhinorrhea/sinusitis
Age at end of chemotherapy treatment	29 month old	29 month old	31 month old	33 month old	24 month old
Course after chemotherapy treatment	CMV viremia and cystitis, *Clostridium difficile* colitis, *Mycobacterium chelonae* cellulitis	Clostridium difficile colitis, oral herpes simplex virus, norovirus, bocavirus, rhinovirus, and HHV-6 viremia, Enterobacter cloacae cystitis, pneumatosis intestinalis	*Mycobacterium chelonae* abscesses, parainfluenza-3, coronavirus, CMV retinitis, *Candida esophagitis*	Pulmonary aspergillus, *Pseudomonas* sepsis	Parainfluenza type 3 sinusitis, HHV-6 viremia, and encephalitis
Age immunodeficiency confirmed	31 month old	31 month old	44 month old	36 month old	31 month old
Therapy after ALL treatment	None	Interleukin-7	HSCT	None	HSCT
Current age or age at death	31 month old (deceased)	35 month old (deceased)	50 month old (deceased)	37 month old (deceased)	8-year-old (alive)
Autopsy results	Disseminated aspergillosis; severe thymic involution; lymphoid depletion	Diffuse bronchopneumonia; severe thymic involution, lymphoid depletion	Diffuse alveolar damage	Autopsy not performed	Not applicable

ALL, acute Lymphoblastic leukemia; MLL, mixed lineage leukemia gene; MLL-R, MLL rearranged; COG, Children's Oncology Group; CCG, Children's Cancer Study Group; HSCT, hematopoietic stem cell transplant. CMV, cytomegalovirus; HHV-6, human herpesvirus 6.

[a]Treated before induction amendments.

[b]Treated after induction amendments (elimination of cyclophosphamide 1 g/m^2).

she tested negative. Patients A and C had normal newborn screening for SCID, using T-cell receptor excision circle (TREC) assays. All patients were HIV-negative before and after treatment.

After chemotherapy, patients were mildly to severely lymphopenic and developed recurrent or persistent infections. All were identified through formal immunology consultation to have a non-HIV acquired immunodeficiency between 2 and 13 months, median 3 months, after completing chemotherapy (Table 2). Three patients received additional therapy (one with interleukin-7 [IL-7] and two with HSCT) once the immunodeficiency was recognized. Unfortunately, four of the patients died with severe infections. Patient E was successfully treated with an unconditioned 10/10 HLA-matched unrelated donor HSCT.

3 | DISCUSSION

We describe the first report of non-HIV, persistent T-cell immunodeficiency, with varying B-cell and NK-cell depletion, in patients with infant ALL following modern intensive chemotherapy. Patients in our cohort remained mildly to severely lymphopenic and flow cytometry demonstrated extremely low $CD3^+$, $CD4^+$, and $CD8^+$ T-cell populations consistent with a severe T-cell immunodeficiency despite completion of their chemotherapy treatment 2–13 months prior. We believe it is very unlikely that our patients had unrecognized PID. None of these patients had strong identifiers of PID, such as failure to thrive or intravenous antimicrobial use prior to ALL diagnosis.[10] Patient B did have a distant family history of RAG2 deficiency but she did not carry this mutation. Investigations prior to starting chemotherapy suggested patients A, B, and C had been exposed to viral infections with no major complications. Finally, Patient E had an extensive genetic workup excluding common SCID mutations and Patients A and C had normal TREC assays. Based on the described history and investigations, we concluded these were secondary immunodeficiencies produced by the chemotherapy.

Studies of immune reconstitution in children who received chemotherapy for hematologic malignancy demonstrate that in most children total lymphocyte count recovered within 3–6 months.[11] The total B-cell count is normal in most children by 1 month and all children by 6 months after chemotherapy cessation.[6] NK-cells were

TABLE 2 Immunologic investigations assessing immune function and causes of immune deficiency

	Patient A	Patient B	Patient C	Patient D	Patient E	Normal range[7–9]
Investigations at ALL diagnosis						
ALC (cells/μl)	14,600	12,700	0	n/a	n/a	3,400–9,000
IgG (g/l)	5.61	2.15	8.27	n/a	n/a	2.4–8.8
Abnormal viral serology	CMV IgM positive, CMV IgG positive	EBV IgG positive	CMV PCR positive	n/a	None	
Investigations after completion of chemotherapy treatment						
Time since completion of chemotherapy treatment	2 months	2 months	13 months	3 months	7 months	
ANC (cells/μl)	2,389	2,400	882	21,597	4,290	2,000–7,100
ALC (cells/μl)	210	1,400	82	n/a	1,670	2,300–5,400
$CD3^+$ (cells/μl)	82 (39%[a])	14 (1%)	25 (38%)	n/a (1.7%)	<17 (<1%)	1,400–3,700 (56–75%)
$CD4^+$ (cells/μl)	4 (2%)	14 (1%)	<20 (<1%)	n/a (0.5%)	<17 (<1%)	700–2,200 (28–47%)
$CD8^+$ (cells/μl)	67 (32%)	0 (0%)	23 (35%)	n/a (0.7%)	<17 (<1%)	490–1,300 (16–30%)
$CD19^+$ (cells/μl)	23 (11%)	1,065 (74%)	<20 (<1%)	n/a (1.6%)	1,486 (89.9%)	390–1,400 (14–33%)
$CD56^+$ (cells/μl)	84 (40%)	187 (13%)	41 (62%)	n/a (93.7%)	167 (10.1%)	130–720 (4–17%)
IgG (g/l)	4.91	2.07	2.89	2.13	<0.33	7.1–11.6
Other	TRECs normal	*RAG2* gene normal	TRECs normal	None	*IL7RA*, *JAK3*, *DCLRE1C*, *ADA* genes and PNP activity, all normal	

ALL, acute lymphoblastic leukemia; ALC, absolute lymphocyte count; IgG, immunoglobulin G; CMV, cytomegalovirus; EBV, Epstein-Barr Virus; PCR, polymerase change reaction; IgM, immunoglobulin M; TREC, T-cell receptor excision circles; *RAG2*, *IL7RA*, *JAK3*, *DCLRE1C*, and *ADA* are common mutations that cause severe combined immunodeficiency; PNP, purine nucleoside phosphorylase deficiency; n/a, information not available.
[a]Percentage of absolute lymphocyte count.

initially thought to totally recover within 1 month of cessation, but more recent studies have shown a delayed drop that may take 6–12 months to fully recover.[6,12,13]

As for the T-cells, recovery of the $CD4^+$ subset has been shown to have a direct relationship to the intensity of therapy and an inverse relationship with age.[14] This inverse relationship is thought to be because $CD4^+$ T-cells recover more rapidly through a thymic-dependent pathway. Normal thymic involution does not begin until approximately 7 years of age.[4] Thymic enlargement post chemotherapy has been demonstrated in pediatric patients.[6] In most children treated for standard-risk and high-risk ALL, $CD4^+$, and $CD8^+$ T-cells require 3–18 months to recover and the $CD3^+$ count at 1 month was greater than 300 cells/μl regardless of treatment intensity.[5,6] Despite these prolonged impairments in immune function, severe opportunistic infections are not typically appreciated after cessation of chemotherapy, and death from infection is rare.[13] These T-cell recovery patterns were not seen in our patients.

In addition, cyclophosphamide and cytarabine have been associated with depletion of early lineage T-cells, thus affecting T-cell proliferation.[15] Although Patient A was treated prior to cyclophosphamide being eliminated from AALL0631 induction, all of our patients were exposed to cumulative cyclophosphamide doses at least double that of standard-risk or high-risk ALL protocols used in older children.[1] It is possible that these higher doses of cyclophosphamide (and cytarabine exposure) contributed to poor T-cell recovery. None of the studies examining immune reconstitution after chemotherapy have focused on infants; thus the pattern of immune recovery compared to older children is unknown.

All of our patients had severe T-cell deficiency with a $CD3^+$ count less than 100 cells/μl, despite some being only mildly lymphopenic. The patients who underwent autopsy were found to have profound thymic involution, suggesting damage to the thymus, which likely contributed to poor T-cell recovery. Patient B was treated with IL-7 because of previous reports in patients post-HSCT or with HIV that $CD4^+$ T-cells recovered with IL-7 therapy.[16–19] Unfortunately, despite this treatment, her T-cells showed no signs of recovery.

These are the first reported cases of non-HIV, severe, persistent T-cell immunodeficiency, with varying B-cell and NK-cell depletion, secondary to infant ALL chemotherapy. These children may benefit from preemptive and aggressive infection management and/or require therapies to assist with immune reconstitution, such as HSCT. However, the prevalence of this complication is unknown. Formal evaluation to identify abnormal T-cell recovery should be considered in all patients with infant ALL following modern intensive chemotherapy protocols.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
HSCT	hematopoietic stem cell transplantation
PID	primary immunodeficiency
SCID	severe combined immunodeficiency
TREC	T-cell receptor excision circle

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