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Atypical presentation of *RAG1*-associated SCID: diagnostic challenges beyond infections and lymphocyte count

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Abbreviations:
ALC: Absolute lymphocyte count
GvHD : Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
IEI : Inborn Errors of Immunity
IgE : Immunoglobulin E
MAIT : Mucosal associated invariant T
NBS : Newborn screening
PHA : Phytohemagglutinin
RAG : Recombinase activating gene
SCID : Severe combined immunodeficiency
TRECs : T-cell receptor excision circles

Article Summary

An infant presented with thrombocytopenia, petechial rash, and a normal lymphocyte count. Immunophenotyping revealed absence of naïve T and B cells with circulating maternal T cells, and RAG1-related SCID was confirmed, requiring early hematopoietic stem cell transplantation and highlighting the importance of suspecting IEI despite normal lymphocyte counts.

Contributors Statement Page

Dr Frédéric Brillant-Marquis collected data and drafted the initial manuscript.

Drs Pauline Tibout, Roseline Thibeault, Isabel Fernandez, Sonia Cellot and Florence Cayouette critically reviewed and revised the manuscript.

Dr Louis Marois coordinated and supervised data collection and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

De-identified data supporting the findings of this case report are available from the corresponding author upon reasonable request and with appropriate institutional approvals, where required, in accordance with local privacy and ethics regulations.

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Severe combined immunodeficiency (SCID) is a rare genetic disorder characterized by profound T lymphocyte defects, often associated with quantitative or functional abnormalities B and/or NK cells, resulting in a failure of adaptive immunity. If untreated, SCID is universally fatal due to severe and opportunistic infections. Beyond infections, SCID may also present with immune dysregulation and non-infectious manifestations, particularly in genetic contexts allowing residual or aberrant T-cell development (1).

Newborn screening (NBS) using T-cell receptor excision circles (TRECs) has been implemented in many regions and has markedly improved early diagnosis and survival. TRECs are small circular DNA fragments generated during thymic T-cell receptor (TCR) rearrangement and reflect recent thymic emigrants. Low or absent TRECs reliably identify conditions characterized by absent naïve T cells, including classical T-cell–negative SCID as well as T^+ SCID phenotypes such as Omenn syndrome and maternal T-cell engraftment, in which circulating T cells may be present despite absent thymic output (2).

Biallelic defects in *Recombinase activating gene* (*RAG*) *1 or 2* impair V(D)J recombination, preventing formation of functional TCRs and B cell receptors (BCRs) and classically resulting in a T-B-NK+ SCID phenotype (3). Hypomorphic or compound heterozygous variants may allow limited or dysregulated lymphocyte development, producing a spectrum of phenotypes including classical SCID, Omenn syndrome, leaky SCID, combined immunodeficiency with autoimmunity, and maternal T-cell engraftment (3).

Omenn syndrome is characterized by oligoclonal proliferation of autologous activated T lymphocytes, leading to severe inflammation with erythroderma, lymphadenopathy,

hepatosplenomegaly, diarrhea, eosinophilia, and elevated immunoglobulin E (IgE) levels. Although most commonly associated with *RAG* mutations, Omenn syndrome may also result from other genetic defects affecting T-cell development (4). In contrast, maternal T cell engraftment reflects persistence of circulating maternally derived allogenic T cells and is considered a highly specific diagnostic feature of SCID in infancy (1).

Here, we report a case of compound heterozygous *RAG1*-associated SCID presenting with autoimmune hematological and inflammatory manifestations despite a normal absolute lymphocyte count (ALC), illustrating the diagnostic challenges of atypical, non-infectious SCID presentations.

The patient was a female infant born at term to non-consanguineous parents, with no relevant family history. She was born prior to the implementation of NBS for SCID in Quebec. Routine immunizations at two months included oral live attenuated rotavirus vaccine followed by a brief self-limited febrile gastroenteritis. She did not receive Bacillus Calmette-Guérin (BCG) vaccination.

At 3.5 months of age, she presented with a two-week history of diffuse rash and preserved general condition. Examination revealed extensive purpura and petechiae with mucosal involvement. Growth parameters were appropriate for age. Oxygen saturation was measured at 84% on room air, without fever and respiratory distress.

Laboratory investigations showed severe thrombocytopenia (14 x 10^9/L) with a normal ALC (7,4 x 10^9/L). Hemoglobin, blood smear and immunoglobulin levels were normal (Table 1A). Chest radiography demonstrated bilateral ground-glass opacities. Rhinovirus was detected by polymerase chain reaction (PCR) in nasopharyngeal and blood samples.

Given the severity of the purpura, broad-spectrum antibiotics were initiated. Thrombocytopenia was refractory to irradiated platelet transfusion but rapidly improve after dexamethasone and intravenous immunoglobulin (1g/kg). She was discharged with a diagnosis of atypical immune thrombocytopenia secondary to viral infection.

She was readmitted weeks later with a diffuse xerotic, squamous erythroderma, most prononced on the face and scalp (Figure 1). Skin biopsy shoeed lichenoid interface dermatitis with epidermal lymphocyte exocytosis.

Immunophenotyping revealed persistently normal ALC but markedly reduced T- and B-cell counts, complete absence of naïve $CD4^+$T cells ($CD3^+$ $CD4^+$ $CD45RA^+$ $CD31^+$) and preserved NK cells (Table 1A). T-cell proliferation to phytohemagglutinin was markedly reduced. Proliferative responses to other mitogens or antigens were not assessed. Mucosal-associated invariant T (MAIT) cells (TCR $Va7.2^+$) and γ/δ T cell expansions were excluded, and TCR Vß analysis demonstrated a highly skewed oligoclonal repertoire (Table 1B). Chimerism analysis of peripheral blood lymphocytes revealed 19% circulating maternally derived T cells, confirming maternofetal T-cell engraftment rather than sample contamination. Regulatory T cells were not specifically quantified. Eosinophilia was present (1,5 x 10^9/L), while serum IgE remained undetectable (<3.6 kUI/L).

Genetic testing identified compound heterozygous pathogenic *RAG1* variants, consisting of a frameshift mutation (c.519del; p.Glu174Serfs*27) and a missense mutation (c.2327G>A; p.Arg776Gln). confirmed in *trans.* Both variants have been previously reported in SCID, with no strict genotype–phenotype correlation.

Further evaluation was performed to assess the extent of organ involvement and to rule out infectious complications. A chest computed tomography (CT) scan revealed bilateral diffuse ground-glass opacities and enlarged axillary lymph nodes. An extensive infectious work-up revealed persistent rhinovirus detected in both bronchoalveolar lavage fluid and nasopharyngeal samples, rotavirus A and norovirus shedding on stool multiplex PCR, and *Toxoplasma gondii* detected by PCR on axillary lymph node biopsy. A comprehensive evaluation for disseminated toxoplasmosis, including PET scan, brain MRI, and ophthalmic examination, was normal. Negative maternal serologic testing excluded congenital or vertically acquired toxoplasmosis, supporting postnatal acquisition in the setting of immunodeficiency. The patient was therefore treated with intravenous trimethoprim-sulfamethoxazole.

Despite antimicrobial therapy, she developed worsening erythroderma, chronic diarrhea transaminase elevation (up to fivefold) and lymphocytosis (up to 19.2 x 10^9/L). Given confirmed maternall T cell chimerism, absence of detectable IgE and lack of Th2-skewing, the presentation was attribuated to maternal T-cell–mediated graft-versus-host disease (GVHD) rather than Omenn syndrome.

Immunosuppression with cyclosporine (target trough levels 150–200 ng/mL) and topical tacrolimus led to partial improvement while addition of methylprednisolone (2 mg/kg/day) resulted in rapid clinical response. She underwent haploidentical TCRαβ- and CD19- depleted HSCT from her father, following a reduced-intensity conditioning with busulfan, fludarabine and anti-thymocyte globulin. The post-transplant course was uneventful and she was discharged on day +23. Written informed consent for publication

was obtained from the patient's parents, and the study complied with institutional and national ethical standards.

This case highlights the clinical heterogeneity of SCID and demonstrates that immune dysregulation, including autoimmune cytopenias, may precede infectious manifestations, particularly in genotypes allowing residual or aberrant lymphocyte development. Our patient first came to medical attention with autoimmune thrombocytopenia and inflammatory cutaneous manifestations, emphasizing that SCID may initially present outside of immunology settings, including hematology, dermatology, or general pediatrics.

Patients with inborn errors of immunity are known to have a markedly increased risk of autoimmune cytopenias, estimated at approximately 120-fold higher than the general population, with early onset and refractoriness serving as key warning signs (5). In RAG deficiency, defective central tolerance, impaired receptor editing, and abnormal thymic selection contribute to the emergence of autoreactive or alloreactive lymphocytes, predisposing to immune-mediated cytopenias (6, 7). In the present case, the diagnosis of immune thrombocytopenia was supported by isolated severe thrombocytopenia, normal red cell and leukocyte morphology, refractoriness to platelet transfusion, and rapid response to immunomodulatory therapy.

A particularly challenging aspect of this case was the presence of a normal ALC, which may falsely reassure clinicians and delay the diagnosis of SCID. As illustrated here, ALC alone are insufficient to exclude severe T-cell immunodeficiency, and detailed immunophenotyping—especially assessment of naïve T-cell populations—remains

essential when clinical suspicion persists. This case reinforces the importance of evaluating immune function rather than relying solely on quantitative lymphocyte measures.

Genetic analysis revealed compound heterozygous pathogenic variants in *RAG1*, a gene classically associated with a T-B-NK^{+} phenotype. However, *RAG1* deficiency is increasingly recognized as a spectrum disorder, encompassing classical SCID, Omenn syndrome, leaky SCID, combined immunodeficiency with granulomas and/or autoimmunity, and maternal T-cell engraftment**.** Hypomorphic or compound heterozygous variants may permit limited recombinase activity, leading to residual, dysregulated, or oligoclonal T-cell populations, as observed in this patient. (8).

Differentiation between Omenn syndrome and maternal T-cell engraftment is critical for appropriate management (Table 2). In Omenn syndrome, tissue damage is mediated by autologous oligoclonal T cells, typically associated with Th2 skewing, elevated IgE, and eosinophilia (9, 10). In contrast, maternal T-cell engraftment results from allogeneic maternally derived T cells, capable of inducing graft-versus-host disease–like manifestations (11). In our patient, the absence of detectable IgE, lack of clear Th2 features, and confirmation of maternal chimerism strongly supported an alloreactive process rather than Omenn syndrome.

Beyond *RAG* deficiency, other genetic causes of T^{+} SCID must be considered, including defects in *ZAP70*, major histocompatibility complex class II, CD3 subunits, and T-cell signaling pathways. Recognition of these entities is crucial, as they may similarly present with preserved or elevated lymphocyte counts but profound functional impairment (1).

This patient was born prior to the implementation of newborn screening for SCID in Quebec. Under the current screening program, absent naïve T cells would likely have led to early detection, before the onset of autoimmune and inflammatory complications. This highlights the value of NBS and the need for continued clinical vigilance in regions without universal screening.

In conclusion, this case underscores that SCID may present with atypical, non-infectious manifestations, including early autoimmune cytopenias, despite a normal ALC. The identification of circulating maternal T cells highlights the need for comprehensive immunophenotyping beyond lymphocyte enumeration when immune dysregulation is observed in infancy. Clinicians should maintain a high index of suspicion for inborn errors of immunity in infants with early, severe, or refractory autoimmune or inflammatory features, as early recognition remains critical for timely curative intervention.

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Table 1 : Lab investigations

Table 1A : Immunological investigations

Context	ITP	Erythrodermal rash	Reference values
WBC ($x10^9$/L)	14.2	11.1	(5.0-13.0)
Platelets ($x10^9$/L)	14	66	(150-400)
Lymphocytes ($x10^9$/L)	7.4	6.7	(2.1-9.0)
Eosinophils ($x10^9$/L)	0.500	1.500	(0.050 -0.500)
IgG (g/L)	8.16	-	(2.50-9.00)
IgA (g/L)	2.21	-	(0.10-1.80)
IgM (g/L)	0.49	-	(0.20-1.20)
IgE (kUI/L)	-	<3.6	
Lymphocyte subsets			
CD3+ ($x10^6$/L)	-	1876	2500-5600
CD3+ CD4+ ($x10^6$/L)	-	1742	1800-4000
CD4+ CD31+ CD45RA+ (%)	-	0	59 – 84
CD3+ CD8+ ($x10^6$/L)	-	134	590-1600
CD19+ ($x10^6$/L)	-	20	430-3000
CD16+ CD56+ ($x10^6$/L)	-	4797	170-830

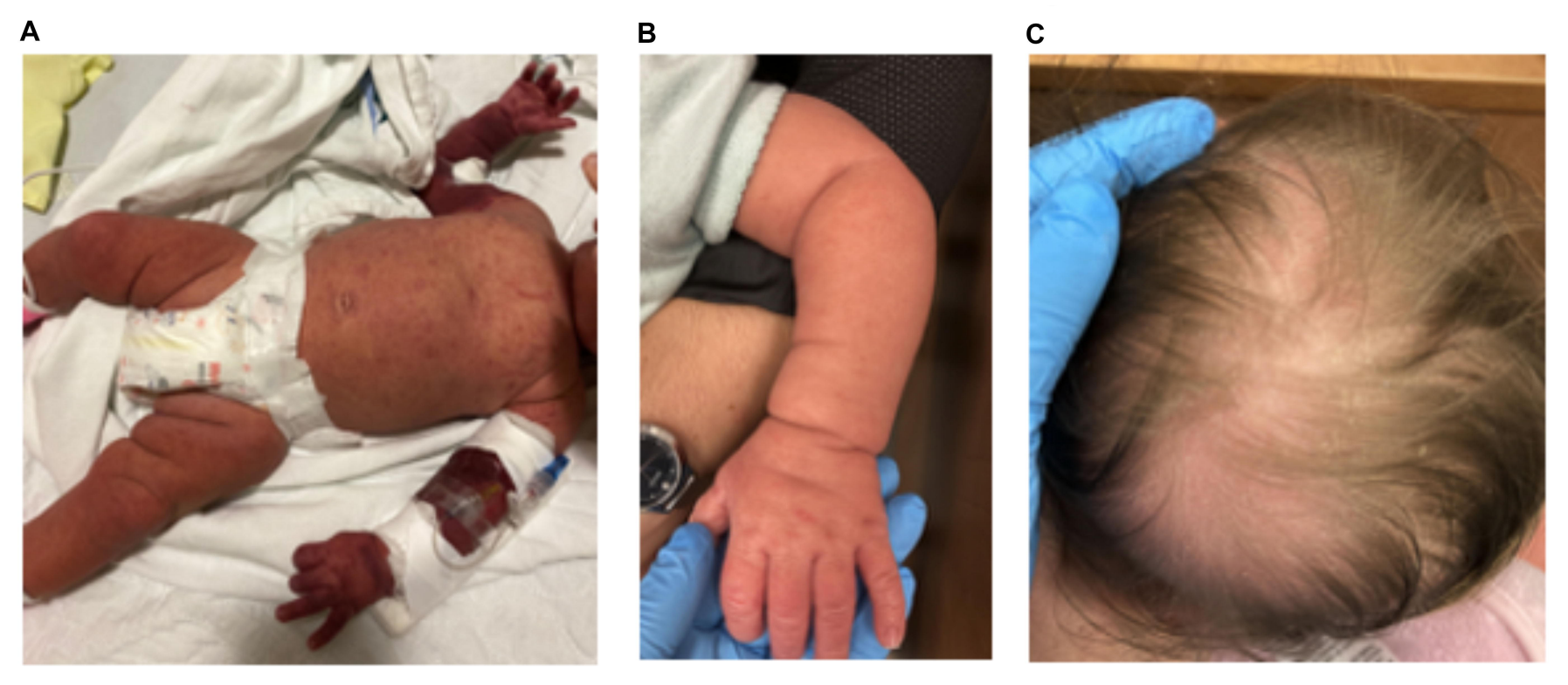
Table 1B : T Lymphocyte Vβ repertoire characterization (% TCR- Vβ families)

TCR- Vβ	% $CD3^+CD4^+$	% Normal Rank $CD3^+$ $CD4^+$	% $CD3^+$ $CD8^+$	% Normal Rank $CD3^+$ $CD8^+$
Vβ 1	4.3	1.8-6.4	1.4	1.2-9.9
Vβ 2	**2.0**	4.5-15.6	**0.4**	1.5-9.0
Vβ 3	**0.1**	0.5-9.0	0.9	0.5-13.3
Vβ 8	**9.5**	1.9-7.3	**9.0**	0.6-8.7
Vβ 9	3.8	1.4-4.3	0.5	0.3-3.3
Vβ 11	**1.9**	0.6-1.4	0.7	0.2-4.2
Vβ 12	**0.4**	1.2-4.0	1.0	0.2-2.7
Vβ 17	**9.2**	3.6-8.1	3.2	0.9-11.7
Vβ 18	**2.2**	0.4-2.0	0.2	0.1-5.2

Table 2. Comparison of Omenn syndrome and maternal T-cell engraftment in severe combined immunodeficiency

	Omenn syndrome	Maternal T-cell engraftment
Pathophysiology	Autologous oligoclonal T cells resulting from defective thymic selection and impaired central tolerance	Allogeneic maternally derived T cells persisting in the infant's circulation
Genetic background	Most commonly associated with *RAG1*/*RAG2* defects, but may occur with other genes affecting T-cell development	Occurs in the context of profound T-cell immunodeficiency, most often SCID
Origin of T cells	Autologous	Allogeneic (maternal)
TCR repertoire	Oligoclonal and highly restricted	Restricted, reflecting maternal T-cell clones
Naïve T cells	Absent or profoundly reduced	Absent (despite presence of circulating T cells)
Absolute lymphocyte count	Normal or mildly elevated	Normal or elevated
IgE levels	Typically elevated	Normal or low
Eosinophilia	Common	Variable; may be absent
Th2 skewing	Frequently present	Absent
Cutaneous involvement	Generalized erythroderma	GVHD-like rash, often erythrodermic
Gastrointestinal involvement	Chronic diarrhea, protein-losing enteropathy	GVHD-like enteropathy, diarrhea
Hepatic involvement	Hepatosplenomegaly, hepatitis	GVHD-like hepatitis with transaminase elevation
Chimerism analysis	Negative for maternal cells	Positive for maternal T-cell chimerism
Diagnostic significance	Represents a form of "leaky" SCID	Highly specific and diagnostic feature of SCID in infancy
Response to immunosuppression	Partial and often transient	Typically responsive prior to curative HSCT

Figure 1. Evolution of cutaneous manifestations in a patient with RAG1-associated SCID and maternal T-cell engraftment.
(A) Purpuric and petechial rash observed at initial presentation during severe thrombocytopenia.
(B–C) Progression to diffuse xerotic and squamous erythroderma during hospitalization, consistent with inflammatory and graft-versus-host disease–like cutaneous involvement.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