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CORRESPONDENCE

A Rare Cause of Double Negative αβ T Cell Lymphocytosis

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Dear Editor

Double-negative (DN) T lymphocytes (CD3 + CD4-CD8- T cell) usually comprise of <2.5% of total lymphocytes in peripheral blood. The most common cause of DN T cell lymphocytosis in children is autoimmune lymphoproliferative syndrome (ALPS) [1]. We describe the case of a child with non- ALPS related DN αβ T cell lymphocytosis.

A 6- month old male child born of a second degree consanguineous marriage presented with a history of generalized eczematous rash, persistent fever, failure to thrive, oral thrush, and 1 episode of pneumonia from 4 months of age. The elder male sibling had died at the age of 3 months due to pneumonia. Physical examination revealed mild pallor, bilateral inguinal lymphadenopathy, and fine crackles in the chest. In view of history of early life sibling death, failure to thrive, and infections, primary immunodeficiency was suspected. Total leukocyte count was 4200/mm^3 with an absolute lymphocyte count of 2436/mm^3 (4000–13,500/mm^3). No thymic shadow was evidenced on chest X-ray. His lymphocyte subset analysis showed 66% T cells (CD4+ T cells: 28%, CD8+ T cells: 13%, double negative T cells [CD3+ αβ + CD4-CD8-T cell]:58%), 26% B cells and 8% NK cells. The CD3 + T cells mainly had αβ TCR and had a memory phenotype (CD45 RO: 97.5%). Most of the double negative (DN) T cells had an αβ T cell receptor (TCR) (Supplementary Fig. 1). Serum immunoglobulin levels were normal except for a raised IgE level of 24,200 IU/ml (Table 1).

Eczematous rash, high IgE levels, and lymphadenopathy raised the possibility of Omenn syndrome. However, a high proportion of DN T cells, absence of B cell lymphopenia, and absence of eosinophilia were not consistent with a diagnosis of Omenn syndrome. Though raised DN αβ T cells pointed towards ALPS the clinical profile of our patient was not matching [2]. Whole exome sequencing revealed a homozygous 5′ splice site proximal variant in intron 2 of CD3D [c.274 + 5G > A(5′ splice site)] with autosomal recessive inheritance. This variant has been reported previously by Gil et al. [3]. The child succumbed to a respiratory infection at 7 months of age before the final diagnosis could be made. Genetic analysis of the parents could not be done.

CD3δ is an invariant chain of T cell receptor complex and is essential for early thymocyte development. Only 19 cases of CD3δ deficiency have been reported in the literature [4]. Immunodeficiency caused by CD3δ defect was first described by Roifman et al. [5] in three children with SCID. Two males presented with acute respiratory distress, viral infections (adenovirus pneumonitis in one, disseminated CMV in other), and succumbed to multiorgan failure before 4 months of age. The third child was a girl who underwent bone marrow transplantation and is alive. All three patients had low total lymphocyte counts (extremely

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Table 1 Lab values in the child

Variable	Reference range	Patient value
Hemoglobin (gm%)	9.5–14 g%	10 g%
Total leukocyte count($\times 10^6$/L)	6000–17,500	**4200**
Platelet count ($\times 10^6$/L)	150,000–450,000	264,000
Absolute lymphocyte count ($\times 10^6$/L)	3900–9000[a]	**2436**
CD 19+ B lymphocytes($\times 10^6$/L,%)	430–3000(11–41%)[a]	633(26%)
CD 3+ T lymphocytes ($\times 10^6$/L,%)	2500–5600(51–77%)[a]	**1607(66%)**
CD 3−/CD 16+ CD56+ NK cells ($\times 10^6$/L,%)	170–830(3–14%)[a]	194(8%)
CD 3+/CD4+ T lymphocytes($\times 10^6$/L,%)	1800–4000(35–56%)[a]	**449(28%)**
CD3+/CD8+ T lymphocytes($\times 10^6$/L,%)	590–1600(12–23%)[a]	**208(13%)**
CD4- CD8-(DN) T cells	1–10%	**58%**
DN αβ T cells (out of total DN Tcells)		**92.64%**
DN γδ T cells (out of total DN T cells)		7.36%
CD45 RO	4–24%	97.5%
IgG(G/L)	0.23–1.41	0.27
IgA(G/L)	0–0.08	0.035
IgM(G/L)	0–0.145	0.036
IgE(IU/L)	0.003–0.424	**24,200**

[a]Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol*. 2003;112(5):973–980

gm% gram percentage, *NK cell* natural killer cell, *DN* double negative, *CD45RO* pan memory T cell, *Ig* immunoglobulin, *G/L* gram per litre, *IU/L* international unit per litre, *αβ* alpha beta, *γδ* gamma delta

Abnormal values are indicated in bold

low CD3 T cells, undetectable CD4 or CD8 T cells), normal B and NK cell count(T-B + NK+), and homozygous mutation in exon 2 of the CD3D gene. The CD3δ defect usually affects both αβ and γδ T cell development [4]. Gil et al. [3] described two patients with a leaky mutation in CD3δ resulting in severe selective αβ T lymphopenia ($T\alpha\beta^{-}T\gamma\delta^{+}B^{+}NK^{+}$) due to possible differential CD3 δ requirement for αβ T cell development as compared to γδT cells. The high number of DN T cells in our patient could be due to the developmental arrest of T cells during their transition from the double-negative to double-positive stage due to CD3 delta deficiency. Though our child had the same variant in the CD3D gene as described by Gil et al., in contrast to that report, our patient had involvement of both αβ and γδ+ve T cells. The exact reason for this disparity is not clear and requires further research. High IgE and eczematous rash could be due to a large number of memory T cells as has been described in Omenn syndrome. Oligoclonal expansion of memory T cells has been shown in a previous report [3].

To conclude, a high percentage of double-negative αβT cells with features of severe combined immunodeficiency or Omenn like phenotype should make one suspect CD3δ deficiency. Early diagnosis and hematopoietic stem cell transplantation may be life-saving [4].

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Availability of Data and Material The patient data is available on request from the corresponding author.

Compliance with Ethical Standards

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

Ethical Statement We obtained informed consent from the parents of the patient. The study on primary immunodeficiency has been approved by the Institutional ethics committee (2014-186-EMP-EXP dated 22 Oct 2014).

References

1. Liapis K, Tsagarakis NJ, Panitsas F et al (2020) Causes of double-negative T-cell lymphocytosis in children and adults. J Clin Pathol 73(7):431–438. https://doi.org/10.1136/jclinpath-2019-206255
2. Oliveira JB, Bleesing JJ, Dianzani U et al (2010) Revised diagnostic criteria and classification for the autoimmune

lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood. 116(14):e35–e40
3. Gil J, Busto EM, Garcillán B et al (2011) A leaky mutation in CD3D differentially affects αβ and γδ T cells and leads to a Tαβ-Tγδ+B+NK+ human SCID. J Clin Invest 121(10):3872–3876. https://doi.org/10.1172/JCI44254
4. Marin AV, Garcillán B, Jiménez-Reinoso A et al (2014) Human congenital T-cell receptor disorders. LymphoSign J 2(1):3–19
5. Dadi HK, Simon AJ, Roifman CM (2003) Effect of CD3delta deficiency on maturation of alpha/beta and gamma/delta T-cell lineages in severe combined immunodeficiency. N Engl J Med 349(19):1821–1828