Omenn Syndrome Associated with Novel Variants in DNA LIGASE I

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INTRODUCTION

- Omenn Syndrome is an atypical form of severe combined immunodeficiency (SCID) in which aberrant autoreactive T cells attack multiple systems.
- DNA Ligase enzymes are essential for rejoining DNA fragments during replication
- **Omenn Syndrome** has been associated with DNA Ligase IV but **only 1 prior case with DNA Ligase 1 (*LIG1*).**
- We present an infant with fatal Omenn Syndrome who was found to have two heterozygous variants of uncertain significance in *LIG1*.

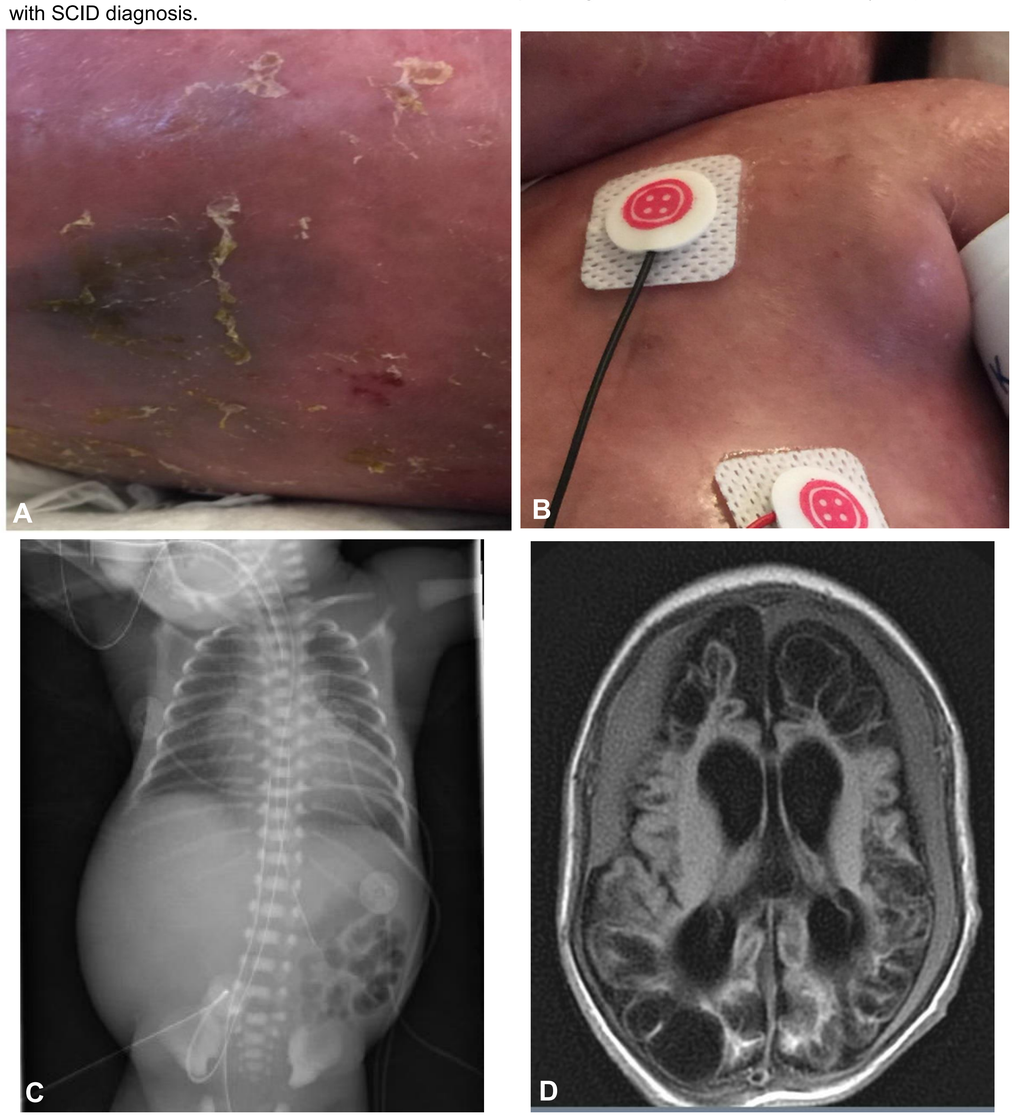
CASE PRESENTATION

- 28-week gestational age male developed rash at 1 month of age- severe exfoliative dermatitis, erythroderma, hair loss, diarrhea, hepatosplenomegaly, and lymphadenopathy.
- Initially normal lymphocyte count and CD3
- Exceedingly low B cells, NK cells, and naïve T cells, consistent with SCID
- Whole exome sequencing (WES) revealed two variants of uncertain significance in *LIG1*
  - **deletion c.1088-2_1094delAGGTCGGCA in exon 13**
  - **c.2312 G>A in exon 24**
- Developed profound cystic encephalomalacia and succumbed to his complications at 5 months of age.

LABS AND IMAGING

Cell Type	Value	Reference Value
Lymphocyte ABS	0.8	2.5 – 16 x 10^3/uL
CD3 %	91.0	32 - 96
CD3 ABS	0.73	2.04 – 6.13 x 10^3/uL
CD4 %	45.0	20.5 – 61.5
CD4 ABS	0.36	1.31 – 3.93 x 10^3/uL
CD8 %	32.0	10.5 – 31.5
CD8 ABS	0.26	0.67 – 2.01 x 10^3/uL
CD19 %	2.0	11.5 – 34.5
CD19 ABS	0.02	0.73 – 2.20 x 10^3/uL
CD56 %	5.0	2.0 – 16.0
CD56 ABS	0.04	0.13 – 1.02 x 10^3/uL
T Reg %	2.0	3.0 – 17.0
T Reg ABS	0.02	0.08 – 0.44 x 10^3/uL
CD4/CD45RA % (Naïve)	7.0	64.0 - 96.0
CD4/CD45RA ABS (Naïve)	0.03	1.68 – 2.51 x 10^3/uL
CD4/CD45RO %	93.0	14.0 – 62.0
CD4/CD45RO ABS	0.33	0.37 – 1.02 x 10^3/uL

TABLE 1. Lymphocyte reconstitution panel demonstrating exceedingly low B cells, NK cells, and naïve T cells. Total CD3 T cell count was normal while naïve T cells expressing CD4/CD45RA were profoundly low, consistent with SCID diagnosis.



IMAGES A. Photograph of patient's skin demonstrating severe desquamation, erythroderma, exfoliative dermatitis. **B.** Photograph demonstrating axillary lymphadenopathy. **C.** Plain chest x-ray film showing little to no thymic shadow, indicating thymic aplasia. **D.** Brain MRI demonstrating extensive cystic encephalomalacia.

DISCUSSION

- Reasoning for considering these variants to be pathogenic:
  - Profound immunological deficits
  - Limited reports of *LIG1* SCID
  - Variant not found in general population
  - No other mutations in known immunodeficiency genes (WES)
- Autoreactive T cell proliferation can make absolute lymphocyte count and total CD3 count appear normal, making diagnosis of Omenn Syndrome increasingly elusive
- This presentation emphasizes the need to include naïve T cell markers when flow cytometry is performed.
  - TREC newborn screening should be correlated with naïve T cell production.
- *LIG1* not currently included on SCID gene panels and was captured only by WES

CONCLUSIONS

What is already known:

- Though rare, *LIG1* deficiency can present with a spectrum of immunodeficiency
  - This is the 9th documented case
- Genetic testing is standard of care for SCID, but *LIG1* is not included on panels

What this case adds:

- Data to extremely limited literature that *LIG1* deficiency can present as fatal SCID
  - 2nd case presenting as Omenn Syndrome
- Emphasizes need for addition of *LIG1* to commercially available SCID gene panels used in newborn screening.

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