CASE REPORT

Recurrent Perianal Abscess in Siblings with CD40LG Mutation: A Diagnostic Clue to Underlying Primary Immunodeficiency

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ABSTRACT

CD40LG deficiency disrupts the interaction between T- and B cells, resulting in defective class-switch recombination and impaired production of IgG, IgA, and IgM. We report two brothers presenting with recurrent perianal abscesses and pneumonia. Their mother had a history of severe perineal abscess with prolonged hospitalization, and a half-brother previously experienced invasive pneumococcal infection, recurrent abscesses and died from septicaemic shock secondary to bacterial laryngopharyngitis. Initial investigations revelaed lymphopenia and hypogammaglobulinemia. Whole exome sequencing identified a hemizygous mutation in CD40LG NM_000074.3:c.415C>T (NP_000065.1:p.Gln139Ter). Both affected siblings were started on immunoglobulin replacement therapy and awaiting for allogeneic hematopoietic stem cell transplantation. The combination of recurrent perianal abscesses, pneumonia, failure to thrive, lymphopenia, hypogammaglobulinemia, and a positive family history highlighted an underlying primary immunodeficiency. This case illustrates the importance of thorough family history assessment, prompt genetic testing, and early initiation of supportive therapies in improving clinical outcomes.
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Keywords: Perianal abscess, CD40LG, Invasive pneumococcal infection, Pseudomonas aeruginosa, Inborn error of immunity

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INTRODUCTION

CD40 Ligand (CD40LG) deficiency is a rare X-linked primary immunodeficiency characterized by defective class-switch recombination, leading to reduced serum levels of IgG, IgA, and IgE, with normal or elevated IgM. The CD40LG gene (OMIM* 300,386) encodes the CD40 ligand, regulating B cell function by interacting with CD40 on the B cell surfaces (1). Pathogenic variants in CD40LG disrupt T–B cell interactions, resulting in impaired immunoglobulin class switching, compromised humoral immunity, and heightened susceptibility to severe, recurrent infections. CD40LG mutation is classified under combined immunodeficiencies in the Table 1 of the Classification from the International Union of Immunological Societies Expert Committee (1). The global incidence of CD40LG deficiency is estimated to be 1 in every 500,000 male livebirths (2). We report two siblings with genetically confirmed CD40LG deficiency who presented with recurrent perianal abscesses, aiming to highlight diagnostic and management challenges encountered in a resource-limited settings.

CASE REPORT

Sibling 1, a three- year old boy, presented with recurrent Pseudomonas aeruginosa perianal abscess requiring multiple incision and drainage procedures, along with failure to thrive (Figure 1 and Figure 2). He first presented at three months of age, with a severe aphthous ulcer, severe iron deficiency anaemia, a urinary tract infection and subsequent nosocomial sepsis.

Sibling 2 first presented at five months of age with recurrent pneumonia requiring intravenous antibiotic treatments and prolonged home oxygen therapy during his first year of life. Multiple positive isolates has been documented across these recurrent pneumonia episodes such as rhinovirus, enterovirus and Respiratory Syncytial Virus (RSV). From one year to five-months of age, he also developed recurrent perianal abscesses (Figure 3).

The mother had a history of severe perineal abscess with prolonged hospitalization in 2018. She also reported that her son from a previous marriage who had invasive

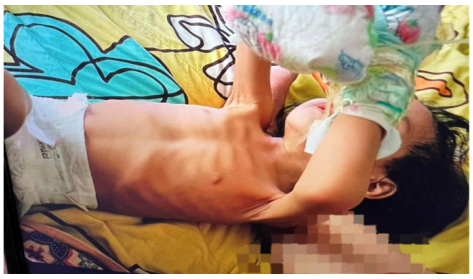

Figure 1: Failure to thrive seen in Sibling 1.

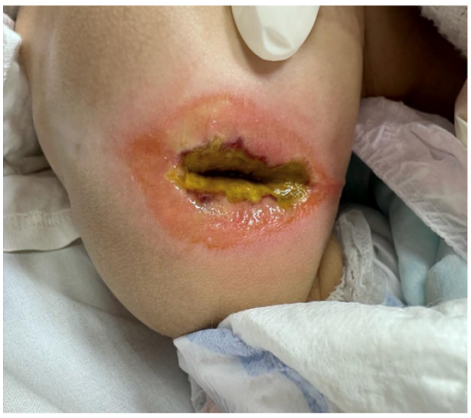

Figure 2: Perianal abscess in Sibling 1.

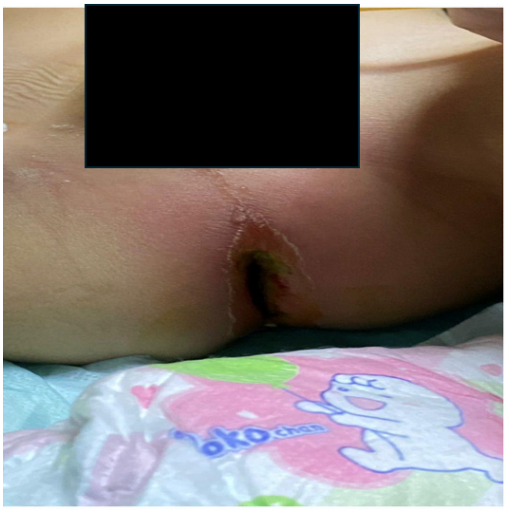

Figure 3: Perianal abscess in Sibling 2.

pneumococcal infection and recurrent abscesses, and died at 3 years and 9 months of age from septic shock secondary to bacterial laryngopharyngitis (Figure 4).

Initial investigations in both affected siblings showed lymphopenia, hypogammaglobulinemia and borderline dihydrorhodamine (DHR) test results (Table I). Whole exome sequencing identified a hemizygous CD40LG variant, NM000074.3:c.415C>T; (NP_000065.1_:p.Gln139Ter), in both siblings. They are currently receiving intravenous immunoglobulin replacement therapy and are awaiting parental decision for allogeneic hematopoietic stem cell transplantation. No further genetic tests was performed for the parent due to funding limitations.

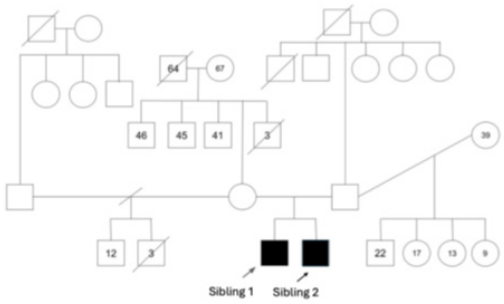

Figure 4: Family tree 3 generations of the CD40LG siblings.

Table I: The list of laboratory investigation results for both siblings upon presentation.

	Sibling 1	Sibling 2
Full blood count with differential counts		
Haemoglobin (g/L) (N: 11.1 – 14.1)	6.1	10.8
White Blood Cell Count ($x10^9$/L) (N: 6.0 – 16.0)	3.29	13.5
Platelet Count ($x10^9$/L) (N: 200 – 550)	396	393
Absolute neutrophil count ($x10^9$/L) (N: 1.0 – 7.0)	0.8	3.45
Absolute Lymphocyte Count ($x10^9$/L) (N: 3.5 – 11.0)	2.0	8.49
Serum Immunoglobulin (g/L)		
IgG (N: 5.01-11.7)	3.96	<0.3
IgA	0.08	<0.05
IgM (N: 0.45-1,78)	1.08	<0.05
Lymphocyte subset enumeration (Absolute count)		
CD3+ T cells (N: 1800-3000)	3008	4302
CD4+ T helper cells (N: 1000-1800)	2112	2738
CD8+ T Suppressor cells (N: 800-1500)	900	1389
CD19+ B cells (N: 700-1300)	996	1368
NK cells (N: 200-600)	65	279
HIV test		
HIV	Non-reactive	Non-reactive
DHR Test (% fluorescent cells)		
Unstimulated	NA	0.9
Stimulated Control	NA	100
Stimulated E. coli	NA	99.2
Genetic test		
Whole Exome Sequencing	Hemizygous mutation in CD40LG NM000074.3:c.415C>T (NP_000065.1_:p.Gln139Ter)	Hemizygous mutation in CD40LG NM000074.3:c.415C>T (NP_000065.1_:p.Gln139Ter)

DISCUSSION

In these cases, both siblings presented with recurrent infections, including perianal abscesses and pneumonia, which are hallmark features of CD40LG deficiency. The

findings of lymphopenia and hypogammaglobulinemia further supported the suspicion of an underlying primary immunodeficiency. The history of severe perineal abscess in the mother and the death of a half-sibling from a similar infection pattern strengthened the likelihood of an inherited immunodeficiency. However, the diagnosis can be delayed due to the variability in clinical presentations, suggesting that genetic modifiers and environmental factors may influence disease severity (3). The absence of cell surface expression of CD40LG on activated CD4+ T cells, using monoclonal anti-CD40L antibodies and flow cytometry, may facilitate the diagnosis of CD40LG deficiency (3). However, the availability of the flowcytometry assay could be restricted across the geographical regions. To facilitate fast diagnosis, early flow cytometry assays for CD40LG expression on the cell surface or genetic testing should be conducted in individuals with recurrent infections and indicative family histories to enable timely management.

The identified mutation (NM000074.3:c.415C>T; NP_000065.1_:p.Gln139Ter) results in a premature stop codon, leading to loss of functional CD40L protein (4). Mutations in CD40LG have been associated with increased susceptibility to infections by encapsulated bacteria such as Streptococcus pneumoniae and Pseudomonas aeruginosa, as seen in these patients. CD40 ligand deficiency results in functional impairments of peripheral neutrophils and has been documented in a significant percentage of CD40L patients, correlating with oral and rectal/perianal ulcers and abscesses (3,4). Multiple literatures have documented the association of pathogens such as giardiasis and cryptosporidiosis with CD40LG deficiency (3).

The principle of therapy for CD40LG deficiency includes intravenous immunoglobulin (IVIG) replacement therapy, antimicrobial prophylaxis to prevent opportunistic infections, prompt and aggressive treatment of infections, and recombinant human granulocyte colony- stimulating factor (rhG-CSF) for individuals with persistent neutropenia (3).

However, hematopoietic stem cell transplantation (HSCT) remains the only curative option, offering long-term immune reconstitution (5). De la Morena et al (2017) reported that early HSCT (before the onset of severe infections and organ damage) significantly improves survival and immune recovery (5). In this case, the parents are still considering the option of HSCT, and counselling should emphasize the long-term benefits of early transplantation alongside the potential risks of delaying the procedure. Gene therapy for CD40LG deficiency is under research but has yet to enter clinical practice.

CONCLUSION

This case highlights the need to maintain a high index of suspicion for primary immunodeficiencies in children presenting with recurrent infections, perianal abscesses, and pneumonia. A detailed family history remains crucial, particularly for identifying patterns suggestive of X-linked disorders such as CD40LG deficiency. Whole exome sequencing plays an important role in in confirming a definitive genetic diagnosis and guiding appropriate treatment strategies. While intravenous immunoglobulin (IVIG) therapy remains the cornerstone for infection control, early hematopoietic stem cell transplantation (HSCT) offers the possibility of a definitive cure. Emerging advances in gene therapy may ultimately offer a durable, disease-modifying alternative for individuals with CD40LG deficiency and other monogenic immune disorders.

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