

## Omenn syndrome- A rare immunodeficiency disorder: A case report

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### Abstract

**Introduction:** Omenn syndrome, a variant of severe combined immunodeficiency disorder, is a rare condition, with few cases reported in literature.

**Case Characteristics:** A three month old female infant presented with recurrent severe infections, chronic diarrhea, severe erythroderma and lymphadenopathy. Immunological work-up revealed agammaglobulinemia, with both B cell and T cell deficiency. Genetic studies were compatible with Omenn syndrome.

**Outcome:** Bone marrow transplantation was planned, but the infant succumbed to complications.

**Message:** In a young infant with recurrent severe infections, characteristic skin lesions and combined immunodeficiency, Omenn syndrome should be suspected.

**Keywords:** Immunodeficiency, Omenn syndrome, Early diagnosis.

### Introduction

Omenn syndrome, a rare autosomal recessive disease, is characterized by symptoms of severe combined immunodeficiency (SCID) associated with erythroderma, hepatosplenomegaly, lymphadenopathy and alopecia. Patients are highly susceptible to infection and develop fungal, bacterial, and viral infections typical of SCID.

Infants with Omenn syndrome typically present shortly after birth, usually by 3 months of age. This is similar to other types of severe combined immunodeficiency (SCID). The characteristic skin findings (red and peeling skin), chronic diarrhea, and failure to thrive often precede the onset of infections.

Life-threatening infections caused by common viral, bacterial, and fungal pathogens occur next, followed by Lymphadenopathy and hepatosplenomegaly, both symptoms unique to Omenn syndrome.<sup>1</sup>

The prognosis may be improved with early diagnosis and treatment with compatible bone marrow or cord blood stem cell transplantation.<sup>2</sup>

In Omenn syndrome patients, circulating B lymphocytes are usually absent, whereas various numbers of activated and oligoclonal T lymphocytes are present in peripheral blood and infiltrate the skin, gut, liver and spleen, causing a graft-versus-host-like disease

Omenn<sup>3</sup> in 1965 first described reticuloendotheliosis with eosinophilia in several individuals in related sibships from an inbred American family of Irish extraction. Barth et al.<sup>4</sup> concluded that the familial reticuloendotheliosis with eosinophilia described by Omenn is a distinct entity. Pneumocystis carinii, responsible for eosinophilia in other immune deficiency disorders, was not detected in any of Omenn's cases

Schwarz et al.<sup>5</sup> in 1999 illustrated the characteristic erythematous, scaly rash, involving the entire body in an infant with Omenn syndrome. The authors noted that some

clinical hallmarks of the disease, including generalized erythrodermia, lymphadenopathy, massive inflammatory infiltrate leading to pachyderma, and alopecia, are reminiscent of graft-versus-host disease

Khiong et al.<sup>6</sup> characterized mice with a spontaneous mutation in the Rag1 gene and concluded that these mice represent a model for Omenn syndrome.

Marrella et al.<sup>7</sup> generated a knockin mouse model in which endogenous Rag2 was replaced with Rag2 carrying the arg229-to-gln mutation (R229Q; 179616.0002) identified in patients with Omenn syndrome. They concluded that these mice mimic most symptoms of human Omenn syndrome.

Overall, the various forms of SCID are estimated to affect 1 in 75,000 to 100,000 newborns. The exact prevalence of Omenn syndrome is unknown. We share our experience with this rare disorder.

### Case Report

A 3 months old female infant was born to non-consanguineous parents, second in birth order, by normal vaginal delivery with no known significant adverse antenatal or perinatal influences. The birth weight was 3kgs and she was breastfed.

The infant presented to hospital at 3 months of age with pain and difficulty in moving right leg. The baby had history of chronic diarrhea and atopic dermatitis followed by desquamation (Fig. 1) which was being managed conservatively, including lactose free formula feeds. However the baby was failing to thrive despite adequate feeding.

She was evaluated and was found to have cellulitis of right leg. Osetomyelitis was ruled out by nuclear scan. USG hip and knee were normal and blood culture done during this admission was sterile. She was managed conservatively and discharged.

One week later child was readmitted with chronic diarrhea and had culture positive sepsis (*Pseudomonas aeruginosa*) requiring IV antibiotics for 2 weeks.

Two weeks later, baby was readmitted with aspiration pneumonia in respiratory failure requiring intubation and mechanical ventilation. She was noted to have profound erythroderma, desquamation, generalized lymphadenopathy and hepatosplenomegaly. Her mentation was normal. Blood culture was sterile during this admission. She was discharged after 7 days of hospitalization.

In view of repeated infections, she was evaluated for suspected immunodeficiency. Her HIV status was negative. Laboratory investigations revealed eosinophilia, anemia, neutropenia and agammaglobulinemia. Two weeks later, the child was readmitted with ear discharge. Aural secretions culture grew *Pseudomonas Aeruginosa* requiring antibiotics for a duration of 2 weeks. In view of recurrent infections, the baby was placed on prophylactic antibiotics. She developed profound erythroderma and desquamation following which baby has developed bronchopneumonia with severe respiratory distress requiring mechanical ventilation.

Further Immunologic and genetic work up was done. Tests revealed agammaglobulinemia, with combined deficiency of B cells and T cells.

Targeted gene sequencing with selective capture and sequencing of the protein coding regions of the genome/genes was performed. DNA extracted from blood was used to perform targeted gene capture using a custom capture kit. Clinically relevant mutations were annotated using published variants in literature and a set of diseases databases - ClinVar, OMIM (updated on 21st November 2018), GWAS, HGMD (v2018.3) and Swiss Var. Common variants are filtered based on allele frequency in 1000

Genome Phase 3, ExAC (v1.0), gnom AD (v2.1), EVS, dbSNP (v151), 1000 Japanese Genome.

Variant description: Two likely compound heterozygous variants were detected in the RAG1 gene (Table 1).

A heterozygous missense variation in exon 2 of the RAG1 gene (chr11:g.36596181A>G; Depth: 38x) that results in the amino acid substitution of Glycine for Arginine at codon 443 (p.Arg443Gly; ENST00000299440.5) was detected (Table 1). The observed variation lies in the recombination-activation protein 1 (RAG1), recombinase domain of the RAG1 protein<sup>8</sup> and a different missense has previously been reported as one of the compound heterozygous variation in a patient affected with Omenn syndrome.<sup>9</sup> The p.Arg443Gly variant has not been reported in the 1000 genomes. The in silico predictions# of the variant are probably damaging by PolyPhen-2 (HumDiv) and damaging (low confidence) by SIFT, LRT and Mutation Taster 2. The reference codon is conserved across species.

A heterozygous missense variation in exon 2 of the RAG1 gene (chr11:g.36596804C>A; Depth: 80x) that results in the amino acid substitution of Lysine for Asparagine at codon 650 (p.Asn650Lys; ENST00000299440.5) was detected.

Based on above evidence, this RAG1 variation is classified as a likely pathogenic variant

Baby was on total parenteral nutrition awaiting matched donor for bone marrow transplantation. Both the parents and sibling were screened for matching but unsuccessful. While awaiting the donor, baby developed severe ARDS and succumbed.

**Table 1:** Genetic testing results- omenn syndrome

Gene Transcript	Location	Variant	Zygoty	Disease (OMIM)	Inheritance	Classification
RAG1 (+) EN5100000299440.5	Exon 2	c.1327A>G (p.Arg443Gly)	Heterozygous	Omenn Syndrome, B cell negative severe combined immunodeficiency, combined cellular and humoral immune defects with granulomas	Autosomal recessive	Likely Pathogenic
	Exon 2	c.1950C>A (p.Asn650Lys)	Heterozygous			Likely Pathogenic

Genetic analysis of the child showed pathogenic variant of Omenn syndrome with B cell negative severe combined immunodeficiency, combined cellular and humoral immune defects with granulomas



**Fig. 1:** Omenn syndrome

Facial photograph reveals extensive erythroderma with desquamation

### Discussion

Omenn syndrome (OMIM#603554), B cell-negative severe combined immunodeficiency (OMIM#601457) and combined cellular and humoral immune defects with granulomas (OMIM#233650) are caused by mutations in the *RAG1* gene (OMIM\*179615). Omenn syndrome is characterised by lymphadenopathy, increased frequency of bacterial, viral, and fungal infections, severely altered lymph node architecture, depletion of lymphocytes and increased proportion of interdigitating reticular cells and eosinophils. Severe combined immunodeficiency is primarily characterized by absent B cells, absent peripheral blood B cells, granulomas can appear on skin, tongue, lungs or other tissues and combined cellular and humoral immune defects with granulomas is allelic to B cell-negative, T cell-negative, NK cell-negative severe combined immunodeficiency, which has a more severe phenotype.<sup>10</sup>

Omenn syndrome is caused by a partial loss of RAG gene function and leads to symptoms similar to severe combined immunodeficiency syndrome, including opportunistic infections. The RAG genes are essential for gene recombination in the T-cell receptor and B-cell receptor, and loss of this ability means that the immune system has difficulty recognizing specific pathogens.<sup>11</sup> Omenn Syndrome is characterised by the loss of T-cell function, leading to engraftment of maternal lymphocytes in the foetus and the co-existence of clonally expanded autologous and transplacental-acquired maternal lymphocytes.<sup>12</sup> Omenn syndrome can occasionally be

caused in other recombination genes, including *IL-7R $\alpha$*  and *RMRP*.<sup>13</sup>

The differential diagnosis of the Omenn syndrome include severe atopic dermatitis, graft vs. host disease (GVHD), Hyperimmunoglobulin E (HIE) syndrome, and histiocytosis X. Laboratory findings include hypereosinophilia and hypogammaglobulinemia. IgE serum levels are usually increased in the absence of detectable B lymphocytes in peripheral blood, skin and lymph node tissues. Lymphocyte stimulation with mitogens, phytohaemagglutinin (PHA), concavalin A (con A) and Pokeweed Mitogen (PWA) are absent or profoundly reduced.<sup>2</sup>

The recombination activating enzymes RAG1 and RAG2 are mandatory in the assembly of V (D) and J segments. The gene comprises 2 exons; encodes 1043 amino acid protein with ATG start codon present with exon 2. Most of the Omenn syndrome patients have mutation in recombination activating genes RAG1 and RAG2 which have been mapped to chromosome 11p13. This enzyme plays an important role in process of assembling the V (D) and J (Variable, Diversity, and Joining) segments which led to generation and development of both B and T cells. So, impaired effective V (D) and J recombination will lead to markedly reduced number of T and B lymphocyte.<sup>14</sup>

This child presented with classic features of Omenn syndrome, starting with progressive diffuse erythrodermic scaly rash, failure to thrive, recurrent infections, developed generalized lymphadenopathy, hepatosplenomegaly and succumbed to recurrent infections.

The outcome in this disorder is better if diagnosis is made earlier, and early treatment is initiated. Available treatment options include bone marrow transplantation or cord blood stem cell transplantation. Overall the mortality rate remains high.

In our case, early diagnosis was made but the infant died awaiting a matched donor for bone marrow transplantation.

### Conclusion

Omenn syndrome is a rare and fatal immunodeficiency disorder if undiagnosed and left untreated. Early diagnosis and initiation of treatment is associated with better outcomes. Nutritional support involving prolonged parenteral nutrition can be considered awaiting the transplantation. Available treatment options include bone marrow transplantation or cord blood stem cell transplantation. However mortality rate in this disorder is high which can be reduced if diagnosis is established earlier and specific treatment initiated. Being a rare disorder, increasing awareness of the condition would lead to early diagnosis and treatment with improved outcomes in the unfortunate babies afflicted with Omenn syndrome.

**Conflict of Interest:** None.

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