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Omenn Syndrome in an Infant: A Case Report

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Abstract

Background: Primary immunodeficiency disorders are considered in scenarios of recurrent infections with early onset, in an optimally nourished infant. Omenn syndrome, an autosomal recessive, rare type of severe combined immunodeficiency disorder, has been reported with varied clinical manifestations. Here, we report an infant suspected of congenital immunodeficiency whose genetic analysis revealed Omenn syndrome, without manifesting all the typical phenotypic features of this condition.

Clinical Description*:* A five-months old female infant, born out of consanguineous marriage, presented with recurrent episodes of respiratory distress requiring multiple hospitalizations. She subsequently developed persistent diarrhea, extensive perianal and gluteal dermatitis, respiratory worsening with fulminant septicemic shock.

Management: Supportive treatment with intravenous fluids, mechanical ventilation, antibiotics, inotropes were started. A hypoallergenic diet was also administered by naso-gastric route. Considering a background of consanguinity, early age of onset and recurrent symptoms with an acutely worsening clinical course, a genetic work up sent for primary immunodeficiency. It showed a contiguous deletion spanning genomic location encompassing DCLRE1C gene in chromosome 10 was detected, suggestive of a likely pathogenic variant of Omenn syndrome. Despite all measures, the infant succumbed to the disease.

Conclusion: By reporting this case, we intend to highlight that genetic evaluation for primary immunodeficiency may reveal some disorders whose classical phenotype may not always be present in the patient under evaluation. This is yet another atypical case of Omenn syndrome.

Keywords: Primary Immune Deficiency, SCID, Severe Combined Immunodeficiency, Recurrent Infections, Dermatitis

Introduction

An early age of onset of recurrent infections in an infant receiving optimal nutrition, raises the suspicion of primary immunodeficiency disorder, especially in the background of consanguinity among parents. Omenn syndrome is one such disorder, which is a rare type of severe combined immnunodeficiency disorder (SCID) [1-3]. Literature shows varied presentations of this condition. We report an infant confirmed genetically to have Omenn syndrome, presenting with atypical features.

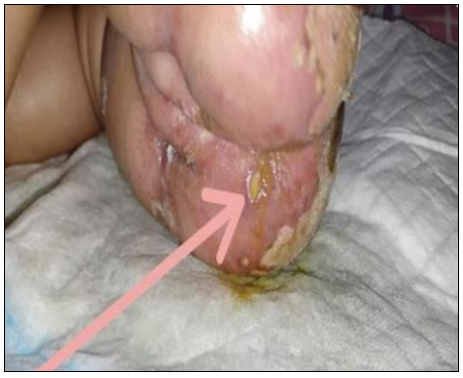


Fig 1: Image showing extensive peri-anal and gluteal erythroderma

Clinical Description:

A five-month-old female infant, born to third-degree consanguineously married parents, was brought with complaints of cough and cold for two months. There was no history of loose stools. She had been hospitalized twice earlier and received nebulization and intravenous antibiotics. She was born at term by a normal vaginal delivery with an uneventful antenatal and natal period. The infant was the first-born child and there is no prior history of abortions in the mother. She was on breastfeeds but had been started on cow's milk since the last two months prior to presentation. Her maternal grandfather had chronic cough requiring long-term metered-dose inhalers.

The infant had an acute onset of fast breathing, with fever and poor feeding for 4 days. On examination, she was found to be febrile with temperature of 100.8-degree farenheit, heart rate of 145/minute, respiratory rate of 64/ minute, with subcostal and intercostal retraction, oxygen saturation of 95 % in room air. She was an otherwise healthy infant, with a weight of 6.5 Kg (birth weight being 3 kg), length of 62 cm and head circumference of 38 cm, all within normal limits with a BCG scar on her left arm. She had no dysmorphic features, no pallor, cyanosis, edema, nor lymphadenopathy. On auscultation, she had wheeze in all lung fields. There was mild hepatomegaly of 4cm below right costal margin, no splenomegaly, but a significant perianal dermatitis attributed to diaper rash. The skin of the child was otherwise normal with normal texture of scalp hair. Cardiovascular and neurological examination was normal.

Management and Outcome:

Based on the history and examination, the differential diagnoses considered were severe pneumonia with sepsis, with a possibility of multi-triggered wheeze, in view of the need for recurrent nebulizations. Investigations done at admission showed white blood cell count 5700 cells/µL with 48% segmented neutrophils, 46% lymphocytes, 5% eosinophils; haemoglobin 10.6/dL; platelet count 382 × 103/µL. Serum electrolytes including serum bicarbonate levels were normal. Arterial blood gas done at admission showed pH of 7.38, Pco2 of 32mmHg and pO2of 82mmHg. Chest X-ray showed normal structure of bone and soft tissue of the chest with presence of thymus. Bilateral lung fields showed increased bronchovascular markings suggestive of a probable viral lower respiratory tract infection.

At admission the Infant was given Levolin Nebulisation for the severe wheeze and 10mg/kg of Injection Hydrocortisone. Oxygen via face mask was started at 5 litres/ minute with FiO2 of 0.4. Injection Ceftriaxone was started after blood culture. However, the respiratory distress worsened with SpO2 of 85% in room air and 92% on face mask oxygen. ABG showing pAO2 of 72mm of Hg, pCO2 of 54mm Hg for which the infant was shifted to a pediatric intensive care unit and was administered high-flow oxygen therapy at 12 litres/minute and Fio2 of 0.45 via humidified high flow nasal canula. A respiratory bio-fire assay was done with the nasopharyngeal swab, which was found to be positive for Rhinoenterovirus. After stabilization, the infant was started on naso-gastric feeding from Day 6 of admission. However, she had multiple episodes of loose stools, for which she required dehydration fluid corrections. A hypoallergenic diet was started via nasogastric tube. The hypoallergenic diet, consisting of an extensively hydrolyzed protein-based formula, was started, considering the possibility of cow's milk-protein allergy causing persistent diarrhea and persistent wheeze in the infant. After introduction of this diet, the stool frequency reduced and the consistency improved. The Infant was also started on Nitazoxanide. However, the peri-anal excoriations had worsened into a well-demarcated pale base ulcer extending over the entire gluteal region, for which plastic surgery opinion was taken and she was managed conservatively.

In the course of time in PICU admission, in view of worsening of respiratory distress she was intubated and started on pressure regulated volume control mode of mechanical ventilation with FiO2 of 0.5, PEEP of 7 and Tidal volume of 35 ml (6ml/kg). Infant was maintaining spo2 of 94% on these settings. After a week of mechanical ventilation, the infant developed pulmonary haemorrhage, identified by bleeding in endotracheal tube, increased oxygen requirement while on mechanical ventilation and chest xray showing diffuse alveolar pulmonary opacities. Blood gas at this point in time showed pH of 7.22, pCO2 of 63mm Hg and pO2 of 56mm of Hg with PF ratio of 86. On day 15 of hospital stay, the infant developed septic shock requiring Adrenaline and Noradrenaline infusion. Serial blood counts have been shown in Table 1. Blood culture showed growth of Acinetobacter and Klebsiella necessitating appropriate antibiotics - Meropenam and Colistin. Thus, the infant was managed on the lines of septic shock.

Table 1: Serial blood cell counts of the infant during course of hospital stay

Investigations	At Admission	Day 5	Day 14	Day 21 (prior to death)
Haemoglobin	11.6 g/dL	10.4 g/dL	6.6 g/dL	9.5g/dL (Post transfusion)
Total counts	5700 cells/ mm3	6600 cells/ mm3	3300 cells/ mm3	970 cells/ mm3
Differential counts	Neutrophil – 48% Lymphocyte – 24% Monocyte – 5% Eosinophil – 1%	Neutrophil – 72% Lymphocyte – 20% Monocyte – 4% Eosinophil – 3%	Neutrophil – 66% Lymphocyte – 28% Monocyte – 4% Eosinophil – 2%	Neutrophil – 56% Lymphocyte – 24% Eosinophil – 4%
Platelet	3.83 lakhs/mm3	4.7 lakhs/mm3	3.33 lakhs/mm3	12000/mm3

Given the multi-system involvement in the form of respiratory, dermatological, and gastrointestinal features with the background of consanguinity and recurrent episodes, with a severe presentation requiring intensive care, a probable diagnosis of primary immunodeficiency was considered. Serum immunoglobulin (Ig) levels were normal, including serum IgE levels. Flow-cytometry of peripheral blood cells could not be done due to non-availability and the status of B-cells, T cells could not be ascertained. Thus, we went ahead with ordering a clinical exome sequencing. On in silico copy number variant analysis, a contiguous deletion of size (~73.0270Kb), spanning genomic location encompassing DCLRE1C gene on chromosome 10 was detected as suggestive of a likely pathogenic variant of

Omenn syndrome with autosomal recessive inheritance pattern.

Despite all efforts, with all supportive treatments, inotropes and antibiotics, for a total of 3 weeks in the pediatric intensive care unit, the infant eventually succumbed to the illness. Parents have been advised of genetic counseling and ante-natal testing in future pregnancies.

Discussion

The infant described above presented with symptoms of recurrent wheeze and persistent diarrhea, commonly seen by pediatricians in their routine practice. However, the recurrent episodes, early age of onset, progressive worsening with multi-system involvement, fulminant course, in the background of consanguinity, raised suspicion of a probable inherited primary immunodeficiency syndrome. Despite inability to perform all required investigations, the confirmatory genetic evaluation clinched the diagnosis of Omenn syndrome.

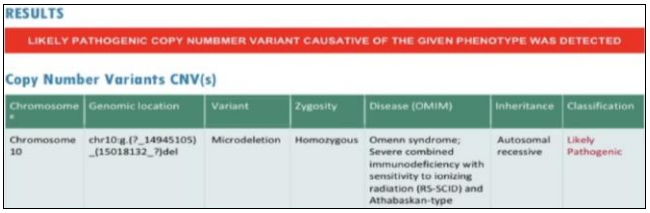
Omenn syndrome is rare autosomal recessive form of severe combined immunodeficiency, with a defining phenotype of T + B-NK + or T-B- NK+. So here, the B cells are usually absent, T-cell counts being normal to elevated, often T cells are activated expressing a restricted T-cell receptor (TCR) repertoire [1-3]. It was first described by Omenn in 1965 [4].

This condition is typically associated with erythroderma, hepatosplenomegaly, lymphadenopathy, and alopecia. Most of the patients present with the classical triad of hepatosplenomegaly, lymphadenopathy, and exfoliative dermatitis with onset from early neonatal period to before 8 weeks of life [3].

Varied types of presentations and associations have been described in the literature, like Omenn syndrome culminating in lymphoma [5], with pathologic changes in skin and bone marrow suggestive of acute graft-versus-host reaction [6], and even a case associated with short-limbed dwarfism due to metaphyseal chondrodysplasia [7]. On the other hand, many classical presentations have been described, like the 5- months old infant, described by Ege, *et al*., with septicemia due to Staphylococcus aureus, failure to thrive, generalised lymphadenopathy, hepato-splenomegaly, and erythrodermatitis [8]. Late-onset presentation between 10 and 36 months of age has also been described in the literature [9].

The diagnosis requires a high degree of suspicion, based on the clinical presentations. Any child presenting in the first year of life with an acute severe illness with pneumonitis and extensive desquamating erythroderma, organomegaly and a background history of recurrent hospital admissions, consanguinity, family history of early sibling deaths, or abortions in the mother, should be suspected to have a primary immunodeficiency disorder [3]. Though our case did not have the typical presentations of Omenn syndrome, there were clinical clues suggestive of an underlying immunodeficiency disorder like recurrent respiratory tract infections, persistent diarrhea, perianal and gluteal erythroderma and excoriations, with fulminant septicemia.

Interpretation of blood cell counts in the disorder may not be straightforward, as lymphocyte counts may be normal or high, unlike in typical SCID. Flow-cytometry analysis of peripheral blood cells revealed lymphocytosis with almost absent B cells as marked by anti CD20. And evidence of abnormal expansion of one or more T-cell clones. Thymus is dysplastic with few remnant lymphoid cells and lymphadenopathy. Immunoglobulins are levels are low, except IgE, which is often raised. Eosinophilia may be observed [10]. We were not able to conduct flow-cytometric evaluation and immunoglobulin levels turned out to be normal, again presenting a diagnostic indecision. Here we need to mention that, though flow-cytometry is an important tool in fetching the diagnosis of primary immunodeficiency, it has its own limitations. The limitations include the incompleteness of the comparability of the genotype and immunophenotype and patients with primary immunodeficiency commonly demonstrate heterogeneous phenotypes, which are not typical for certain genetic abnormalities, therefore, applying a targeted Flow-cytometry panel selected based on the clinician's first impression may result in the disease being missed [11]. Further, normal levels of serum immunoglobulin with normal serum IgE levels and eosinophil levels which has been reported earlier. [12] There have been studies reiterating the importance of whole exome sequencing in patients with Omenn syndrome [13]. Mutations of the recombination activating gene 1 and 2 (RAG1 and RAG2) have been reported in most OS patients and result in the absence of circulating B cells and nonfunctional oligoclonal T cells (12).On the contrary in certain recent studies, not always pathogenic mutation in recombinase-activating genes is the cause of the emergence of a novel mutation [14]. Other genes (DCLRE1C, LIG4, IL7RA, common gamma chain, ADA, RMRP, and CHD7) have also been linked to Omenn syndrome, although less common [8, 15, 16]. In our case, a contiguous deletion spanning genomic location encompassing DCLRE1C gene on chromosome 10 was detected, which likely pathogenic for Omenn syndrome.



RESULTS

LIKELY PATHOGENIC COPY NUMBMER VARIANT CAUSATIVE OF THE GIVEN PHENOTYPE WAS DETECTED

Copy Number Variants CNV(s)

Chromosome	Genomic location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
Chromosome 10	chr10:g.(?_14945105)_(15018132_?)del	Microdeletion	Homozygous	Omenn syndrome; Severe combined immunodeficiency with sensitivity to ionizing radiation (RS-SCID) and Athabaskan-type	Autosomal recessive	Likely Pathogenic

Fig 2: Genetic analysis showing a contiguous deletion of DCLRE1C gene on chromosome 10 suggestive of a likely pathogenic variant of Omenn syndrome with autosomal recessive inheritance pattern

Treatment of the condition is either lymphocyte stimulation tests or bone marrow transplantation, depending upon severity of primary immunodeficiency. Allogenic bone marrow transplantation with HLA-identical and haploidentical marrow can be curative [10]. Such a procedure was not feasible in our set-up, and despite broad-spectrum antibiotics and supportive treatments, the infant could not be saved.

Conclusion

This case, which was confirmed as Omenn syndrome by genetic analysis, presented with recurrent pneumonitis, persistent diarrhea, extensive excoriating perianal and gluteal erythroderma with fulminant septic shock, without the classical picture of hepato-splenomegaly and alopecia. By reporting this case, we intend to highlight that genetic evaluation for primary immunodeficiency may reveal some disorders whose classical phenotype may not always be present in the patient under evaluation.

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