Case report

Unmasking MHC Class II Deficiency: A Novel Mutation in a Child with Pediatric ARDS due to Pneumocystis jirovecii Pneumonia

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Abstract

An 8-month-old boy, the first child of a fourth-degree consanguineous couple with an uneventful past medical history, presented with fever and respiratory distress. He was intubated and managed with high-frequency ventilation. Chest radiography revealed bilateral white-out lungs, and his oxygenation index was 31. Pneumocystis jirovecii was identified through polymerase chain reaction of respiratory secretions. The child was treated with cotrimoxazole and systemic steroids. Due to the severity of the infection caused by an atypical organism, an underlying immunodeficiency was suspected. Genetic analysis revealed a novel homozygous mutation in the RFXANK gene, consistent with major histocompatibility complex class II deficiency. This case represents a rare inborn error of immunity with survival following a severe infection.

Introduction

Major histocompatibility complex (MHC) class II deficiency, also known as 'bare lymphocyte syndrome,' is a rare inborn error of immunity (IEI) [1]. It is characterized by the absence of MHC class II molecules on the surfaces of immune cells, resulting in severe impairment of both cellular and humoral immune responses. Patients with this condition are highly susceptible to infections caused by a broad spectrum of bacterial, viral, fungal, and protozoan pathogens, with the respiratory and gastrointestinal systems being most commonly affected.

We report the case of an infant in whom Pneumocystis jirovecii pneumonia (PCP) led to the diagnosis of MHC class II deficiency with a novel mutation. Although a few cases of MHC class II deficiency have been reported from India, this is the first known child to survive pediatric acute respiratory distress syndrome (pARDS) caused by PCP [2].

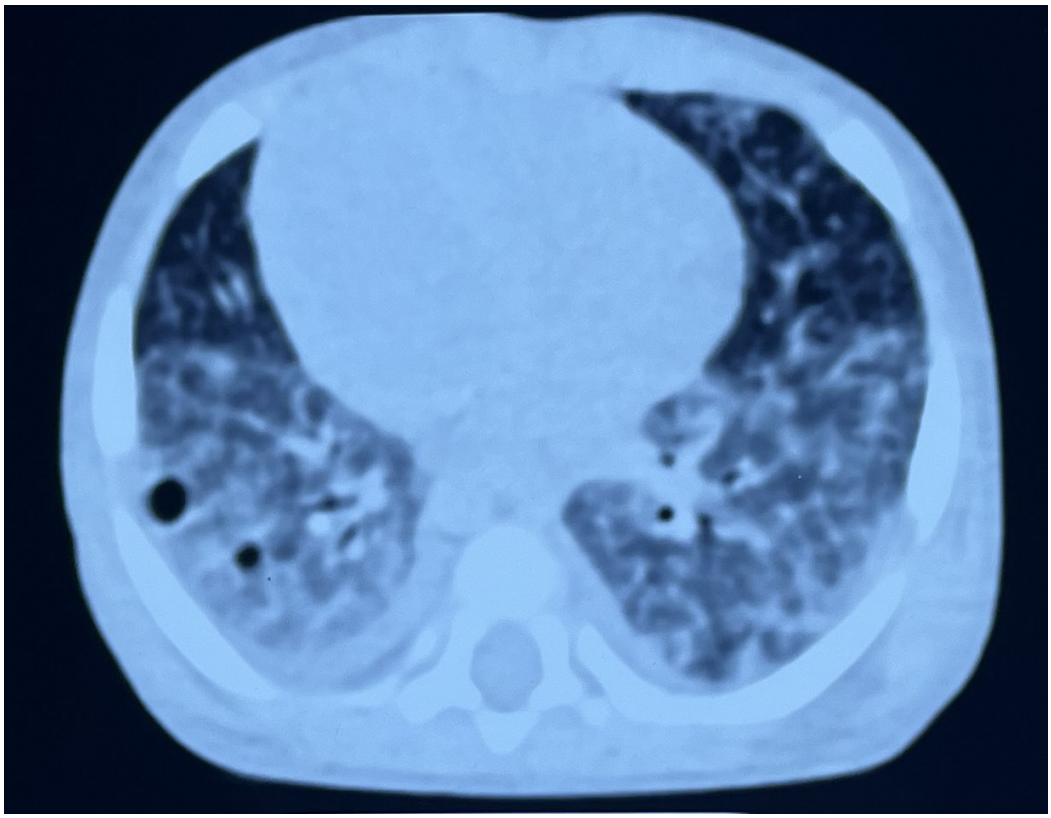
Case Report

An 8-month-old male infant presented with complaints of fever, cough, and fast breathing for five days. He was the firstborn child of a fourth-degree consanguineous couple. His past and birth history were uneventful. He was developmentally normal and had been completely immunized for his age. His anthropometric parameters were within the normal range.

At the time of admission, the child exhibited tachycardia (heart rate: 142/minute), tachypnea (respiratory rate: 78/minute), severe intercostal and subcostal retractions, an audible grunt, central cyanosis, and an oxygen saturation of 71% despite receiving oxygen through a non-rebreathing mask. Chest auscultation revealed diffusely decreased air entry with crepitations. Examination of other systems was unremarkable.

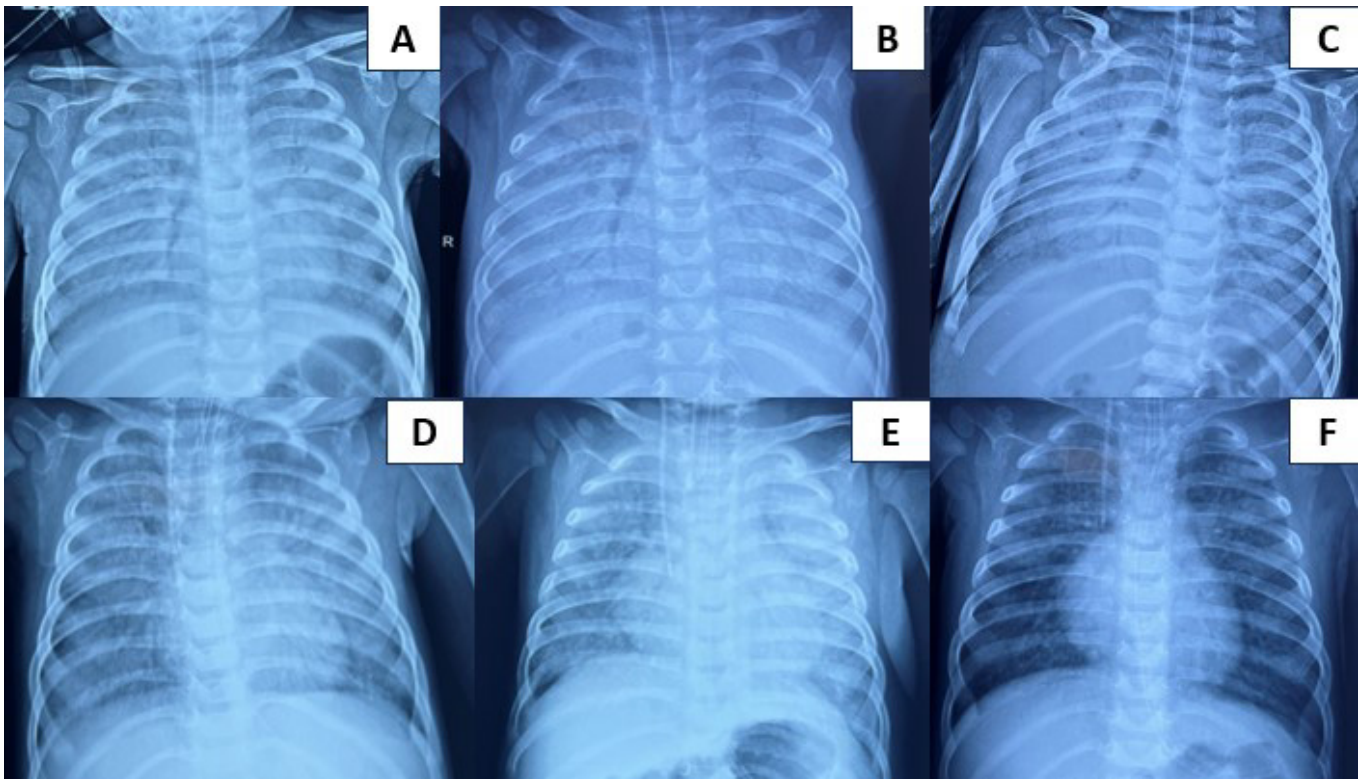
The child was intubated and placed on mechanical ventilation. Arterial blood gas analysis revealed hypoxemia and mixed acidosis (pH: 7.0, pO2: 42 mmHg, pCO2: 79 mmHg, HCO3: 18 mEq/L) with an oxygenation index (OI) of 31. A diagnosis of acute respiratory distress syndrome (ARDS) was made. Due to the failure of conventional ventilation, the child was transitioned to high-frequency ventilation (HFV). Empirical intravenous (IV) antibiotics- piperacillin-tazobactam (300mg/kg/day), and vancomycin (60mg/kg/day) were initiated. The hemogram revealed eosinophilic leucocytosis (total count: 34 × 10^3/L, with differential counts of neutrophils 68%, lymphocytes 8%, and eosinophils 18%). Peripheral smear examination showed no atypical cells. Inflammatory markers, including C-reactive protein (CRP: 68 mg/dL) and erythrocyte sedimentation rate (ESR: 25 mm/hour), were elevated, as was serum lactate dehydrogenase (LDH: 874 U/L). Renal and liver function tests were normal. Blood and urine cultures were sterile. Chest radiography revealed bilateral homogeneous opacities, consistent with a white-out lung. Contrast-enhanced computed tomography (CT) showed diffuse confluent areas of airspace opacifications with surrounding ground-glass attenuation in the bilateral lung parenchyma, interspersed with multiple cystic lesions (Figure 1).

Figure 1: Computed tomography of thorax depicting diffuse, confluent areas of air space opacifications with surrounding ground-glass attenuation affecting both lungs, along with multiple interspersed cystic lesions.



Polymerase chain reaction (PCR) of respiratory secretions identified Pneumocystis jirovecii. Consequently, IV cotrimoxazole (Trimethoprim at 20mg/kg/day) and systemic corticosteroid (prednisolone at 1mg/kg/day) were initiated. The child's clinical and radiographic parameters gradually improved. Serial chest radiographs are shown in Figure 2.

Figure 2: Serial chest radiographs showing the gradual clearance of parenchymal infiltrates.



After 9 days on HFV, he was transitioned to conventional ventilation and extubated on day 12. He was discharged after completing 21 days of IV cotrimoxazole.

The occurrence of a severe atypical infection raised suspicion of an underlying immunodeficiency. Serum immunoglobulin (Ig) levels were measured during a follow-up visit and revealed the following: IgG 92.2 mg/dL (normal range: 217–904), IgM 17.7 mg/dL (normal range: 34–126), IgA 1.1 mg/dL (normal range: 11–90), and IgE 22.2 IU/mL (normal range: 0.76–7.31). Whole exome sequencing identified a homozygous single-base pair deletion in exon 6 of the RFXANK gene (chr19:g.19197565del; Depth: 33x), resulting in a frameshift and premature truncation of the protein 76 amino acids downstream of codon 128 (p.Leu128SerfsTer76; ENST00000303088.9) leading to a diagnosis of MHC class II deficiency. Parental genetic testing was recommended. The parents were counseled on the importance of prenatal genetic testing for subsequent pregnancies. The child was referred for hematopoietic stem cell transplantation (HSCT). He had non-specific viral infections twice in the three-month follow-up. Respiratory symptoms did not recur after the discharge.

Discussion

MHC Class II deficiency is classified under combined cellular and humoral immunity as per the latest IEI classification [1]. MHC Class II molecules, also known as human leukocyte antigens, present exogenous peptides to the T-cell receptors on CD4+ T helper cells, thus playing a crucial role in developing a normal adaptive immune response. Mutations in the genes encoding the MHC class II transactivator (CIITA), regulatory factor X-associated protein (RFXAP), regulatory factor X-5 (RFX5), and ankyrin repeat-containing regulatory factor X (RFXANK) have been linked to the bare lymphocyte syndrome phenotype [3]. It is inherited in an autosomal recessive manner and is predominantly seen in the Mediterranean basin. This form typically has a milder course than other severe combined immunodeficiency syndromes, with the immune system retaining some functionality. This is evidenced by the presence of lymphocytes, positive lymphocyte proliferation in response to phytohaemagglutinin, and, in some cases, detectable levels of immunoglobulins [4]. The presentation begins in infancy with recurrent infections of the respiratory and gastrointestinal tracts along with septicemia. Frequently isolated organisms are Pseudomonas, Salmonella, E. coli, Streptococcus species, enterovirus, cytomegalovirus, herpes simplex virus, Candida

species, Giardia lamblia, and Cryptosporidium parvum [5].

pARDS is a clinical condition resulting from the disruption of the alveolar endothelial barrier, unrelated to cardiogenic pulmonary edema. Direct injury to the alveolar epithelium by infectious agents causing pneumonia is considered as the most common cause. The mortality rate of pARDS is as high as one in four cases [6]. PCP is an opportunistic fungal infection in MHC-II deficiency associated with high mortality. Diagnosis of PCP is multifactorial and may include clinical suspicion, patient risk factors, laboratory evaluation especially elevated LDH, chest computed tomography and definitive diagnosis requires detecting and identifying the organism by PCR assays of respiratory specimens.

Although MHC-II deficiency is less severe than severe combined immunodeficiency, most patients do not survive beyond early childhood. Supportive care, including IVIG and antibiotic prophylaxis, may extend survival only until early childhood. HSCT is regarded as the only curative treatment for this condition. Patients who do not undergo HSCT typically have a median survival of four to five years. Unfortunately, MHC class II deficiency patients seem to be at increased risk for developing post-transplant graft vs. host disease [7,8].

In a case series of 5 patients reported from India, all children exhibited disease onset before 6 months of age, with common manifestations including failure to thrive, sepsis, pneumonia, diarrhea, or candidiasis. Only two children had undergone HSCT. The reported mortality was 80% with respiratory failure being the commonest cause [9]. In contrast, our index case remained asymptomatic during the first half of infancy with normal growth and development. Additionally, presentation with PCP pARDS is noteworthy, as it is unreported in Indian children, although it has been documented globally [10].

Managing rare genetic disorders like MHC Class II deficiency carry significant challenges, particularly in resource-limited countries like India. The limited availability and high cost of genetic diagnostic facilities and definitive treatments like HSCT, and lack of newborn screening programs contribute to delayed diagnosis and poor outcomes. Many families face financial constraints leading to difficult access to specialized care and long-term IVIG therapy. Additionally, counseling regarding consanguinity and genetic risks is often limited, further perpetuating the incidence of such disorders. Policies promoting newborn screening, accessible diagnostic facilities, subsidised treatment costs, early genetic counseling for IEI along with awareness among healthcare providers can improve outcomes and reduce the disease burden in resource-constrained settings.

Conclusion

Severe infection with Pneumocystis jirovecii can be the first manifestation of an IEI in an apparently healthy infant with normal growth and development. Detection of such infections should alert clinicians to evaluate for suspected IEI, enabling early diagnosis and intervention in the index case, as well as offering prenatal genetic testing for subsequent pregnancies.

Declaration by authors

Manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work and the information is not provided in another form.

Conflict of interest

None.

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Contributions

AKS, DS, and ABT managed the case, did literature search and drafted the manuscript.

Declarations

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Conflicts of interest

None declared.

Availability of data and material (data transparency)

Not applicable.

Code availability (software application or custom code)

Not applicable.

Consent to participate

Signed informed consent obtained from patient.

Consent for publication

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References

1. Tangye SG, Al-Herz W, et al., Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. DOI: https://doi.org/10.1007/s10875-022-01289-3

2. Aluri J, Gupta M, Dalvi A, et al. Clinical, Immunological, and Molecular Findings in Five Patients with Major Histocompatibility Complex Class II Deficiency from India. Front Immunol. 2018;9:188. DOI: https://doi.org/10.3389/fimmu.2018.00188

3. Gulec Koksal Z, Bilgic Eltan S, et al. MHC Class II Deficiency: Clinical, Immunological, and Genetic Insights in a Large Multicenter Cohort. J Allergy Clin Immunol Pract. 2024;12(9):2490-2502.e6.
DOI: https://doi.org/10.1016/j.jaip.2024.06.046
4. Krawczyk M, Masternak K, Zufferey M, Barras E, Reith W. New functions of the major histocompatibility complex class II-specific transcription factor RFXANK revealed by a high-resolution mutagenesis study. Mol Cell Biol. 2005;25(19):8607-8618.
DOI: https://doi.org/10.1128/mcb.25.19.8607-8618.2005
5. Klein C, Lisowska-Grospierre B, LeDeist F, Fischer A, Griscelli C. Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome. J Pediatr. 1993;123(6):921-928.
DOI: https://doi.org/10.1016/s0022-3476(05)80388-9
6. Wong JJ, Jit M, Sultana R, et al. Mortality in Pediatric Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. J Intensive Care Med. 2019;34(7):563-571.
DOI: https://doi.org/10.1177/0885066617705109
7. Lum SH, Neven B, Slatter MA, Gennery AR. Hematopoietic Cell Transplantation for MHC Class II Deficiency. Front Pediatr. 2019;7:516.
DOI: https://doi.org/10.3389/fped.2019.00516
8. Renella R, Picard C, Neven B, et al. Human leucocyte antigen-identical haematopoietic stem cell transplantation in major histocompatiblity complex class II immunodeficiency: reduced survival correlates with an increased incidence of acute graft-versus-host disease and pre-existing viral infections. Br J Haematol. 2006;134:510–516.
DOI: https://doi.org/10.1111/j.1365-2141.2006.06213.x
9. Aluri J, Gupta M, Dalvi A, et al. Clinical, Immunological, and Molecular Findings in Five Patients with Major Histocompatibility Complex Class II Deficiency from India. Front Immunol. 2018;9:188.
DOI: https://doi.org/10.3389/fimmu.2018.00188
10. Hanna S, Etzioni A. MHC class I and II deficiencies. J Allergy Clin Immunol. 2014;134(2):269-275. DOI: https://doi.org/10.1016/j.jaci.2014.06.001