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Case Report

Paediatrics Section

X-linked Severe Combined Immunodeficiency Syndrome with Hereditary Spherocytosis in an Infant: A Rare Case Report

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ABSTRACT

Combined Immunodeficiency is an uncommon and inherited Primary Immunodeficiency Disorder (PID) that affects both cellular and humoural immune function and leads to early death. This case report describes the rare co-existence of X-linked Severe Combined Immunodeficiency (SCID) and Hereditary Spherocytosis (HS), highlighting new mutations, challenges in diagnosis and managing complex paediatric cases. A five-month-old male infant, born through vaginal delivery, presented with persistent fever, respiratory distress and moderate hepatosplenomegaly with a family history of undiagnosed male sibling death at two months of age. Laboratory findings revealed neutrophilic leukocytosis and microcytic hypochromic anaemia. The chest imaging demonstrated diffuse infiltrates, a few unilateral cystic lesions, and an absent thymus shadow. While empirical treatment for pneumonia was initiated, multiplex PCR identified multidrug-resistant *Pseudomonas aeruginosa* and *Serratia marcescens*, along with Rhinovirus infection. Whole Exome Sequencing (WES) revealed a pathogenic mutation in the Interleukin 2 Receptor gamma (IL2RG) gene associated with X-linked SCID, and also mutations linked to HS. Antimicrobial prophylaxis was started, and haematopoietic stem cell transplantation was planned; however, financial constraints hindered the treatment, and the infant died at ten months of age. This case emphasises the importance of meticulous family history and timely genetic testing in infants with persistent infections. Early diagnosis can pave the way for targeted and curative interventions.

Keywords: Coombs negative haemolytic anaemia, Genetic mutations, Immunological evaluation, Persistent pneumonia, Severe infection, Whole exome sequencing

CASE REPORT

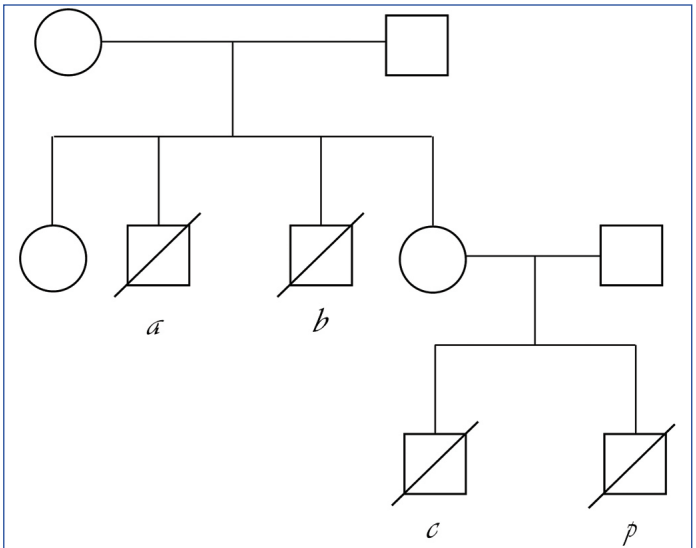
A five-month-old male infant presented to the paediatric emergency with chief complaints of fever for 20 days and difficulty in breathing for 15 days. Fever was remittent with spikes of 101° to 103°F without rash. There was no history of convulsions, diarrhoea, ear discharge, jaundice, or blood transfusion. The infant had been treated for suspected pneumonia at a local hospital for two weeks with little improvement.

He was born at 38 weeks of gestation to a second-gravida mother from a non-consanguineous marriage with a birth weight of 2.7kg (25th percentile) and an uneventful neonatal period. He was exclusively breastfed with normal developmental milestones for his age and was adequately immunised for his age.

In family, his elder brother had died at two months of age after four weeks of hospitalisation due to undiagnosed severe anaemia requiring blood transfusion. Neither parent had any history of blood transfusions or jaundice. Two maternal uncles had also expired due to life-threatening infections within the first five years of life, suggesting an X-linked recessive inheritance pattern [Table/Fig-1].

On examination, vitals were: heart rate 150 per minute, respiratory rate 72 per minute with chest retractions and nasal flaring, blood pressure 68/36 mm Hg, temperature 102°F and oxygen saturation was below 80% on room air. The anthropometric measurements were: weight- 6 kg (50th centile), length- 65 cm (50th centile), and head circumference- 42 cm (50th centile). The infant was sick-looking, with decreased response to tactile stimulus, mild pallor, no lymphadenopathy or dysmorphism. Oral cavity and ear examination were normal. In chest examination, bilateral crepitations and rhonchi were present. The abdomen was soft with hepatomegaly (5 cm, soft, non-tender) and splenomegaly (4 cm, soft). Cardiovascular examination was normal.

With this history and examination findings, the provisional diagnoses of persistent or atypical pneumonia {tuberculosis,



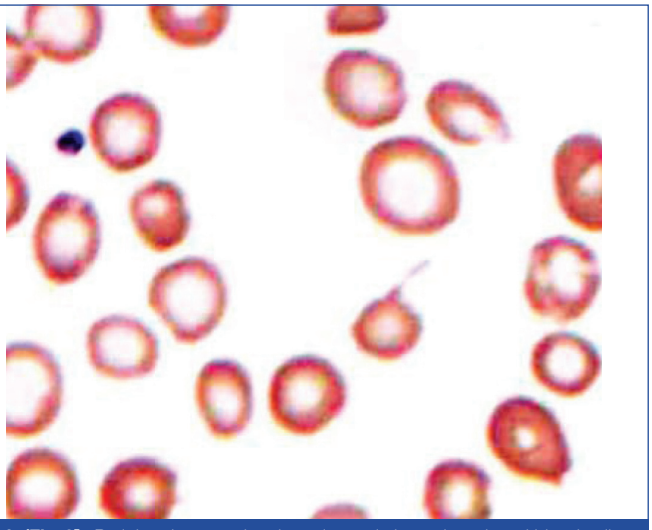
[Table/Fig-1]: Pedigree chart: a) Maternal uncle expired at 2 years of age; b) Maternal uncle expired at 1 year of age; c) Sibling expired at 2 months of age; p) Proband expired at 10 months of age.

Cytomegalo Virus (CMV)} with differential diagnosis of X-linked Primary immunodeficiency diseases (history of early male deaths, severe pneumonia and hepatosplenomegaly), haemoglobinopathy (family history of sibling death due to anaemia) and leukaemia were considered.

Laboratory work-up showed neutrophilic leukocytosis with lymphopaenia [Table/Fig-2]. Peripheral smear showed microcytic hypochromic red blood cells, without any features of haemolysis or abnormal cells [Table/ Fig-3]. Blood gas analysis showed hypoxaemia with compensated respiratory alkalosis (pH: 7.49, PO_2: 52 mmHg, PCO_2: 30 mmHg, HCO_3: 32 mmol/L) Chest X-ray revealed diffuse infiltrates in both lung fields and an absent thymic shadow [Table/Fig-4].

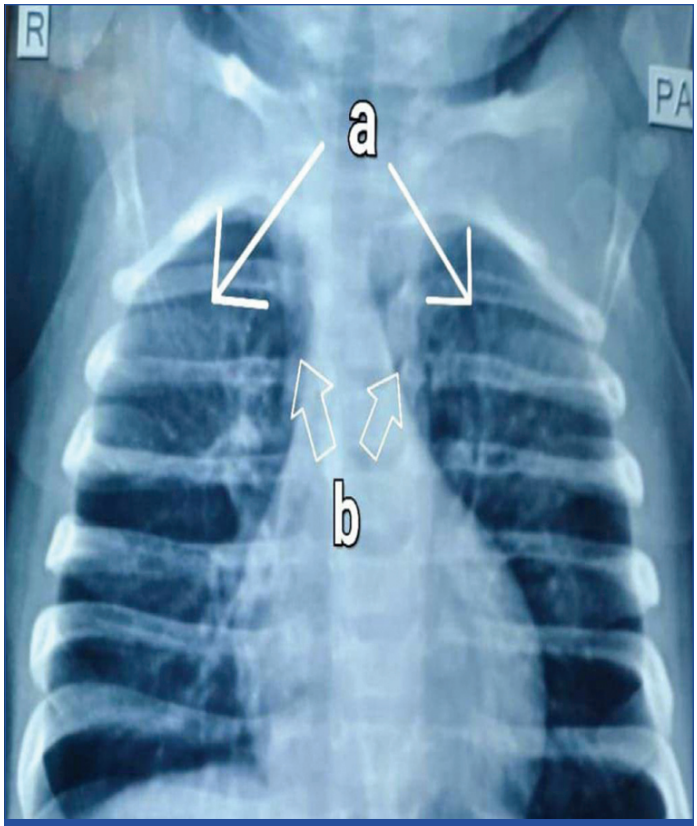
Haematological Investigations		
Investigation	**Patient value**	**Unit**
Haemoglobin	9.4	g/dL
Total leukocyte count	15,300	Cells/mm^3
Differential leukocyte count	Neutrophils 86% Lymphocytes 11% Monocytes 0% Eosinophils 0%	%
Platelet Count	1.2×10^5	Cells/mm^3
Mean Corpuscular Volume (MCV)	69	fL
Mean Corpuscular Haemoglobin Concentration (MCHC)	29.4	g/dL
HS index (MCHC/MCV)	0.42	
Erythrocyte Sedimentation Rate (ESR)	35	mm/hr
Reticulocyte Count	2	%
Direct Coombs Test	Negative	
Haemoglobin electrophoresis	Normal	
Peripheral smear	Microcytic, Hypochromic RBC	
Biochemical Investigations		
Investigation	**Patient Value**	**Unit**
Lactate Dehydrogenase (LDH)	280	IU/L
C-Reactive Protein (CRP)	53.3	mg/L
Serum Sodium	142	mmol/L
Serum Potassium	3.8	mmol/L
Serum Bicarbonate (HCO_3^-)	32	mmol/L
Blood Urea	27	mg/dL
Serum Creatinine	0.7	mg/dL
Total Bilirubin	0.42	mg/dL
Serum Albumin	3.1	g/dL
SGOT (AST)	39	U/L
SGPT (ALT)	42	U/L
Microbiological and Infectious Disease Work-up		
Investigation	**Patient value**	
HIV Card Test	Negative	
Polymerase Chain Reaction (PCR) for Tuberculosis (Gastric Aspirate)	Negative	
Cytomegalovirus (CMV) PCR	Negative	
Malaria Card Test	Negative	
Dengue NS1 Antigen & IgM	Negative	

[Table/Fig-2]: Laboratory investigations.



[Table/Fig-3]: Peripheral smear showing microcytic hypochromic red blood cells.

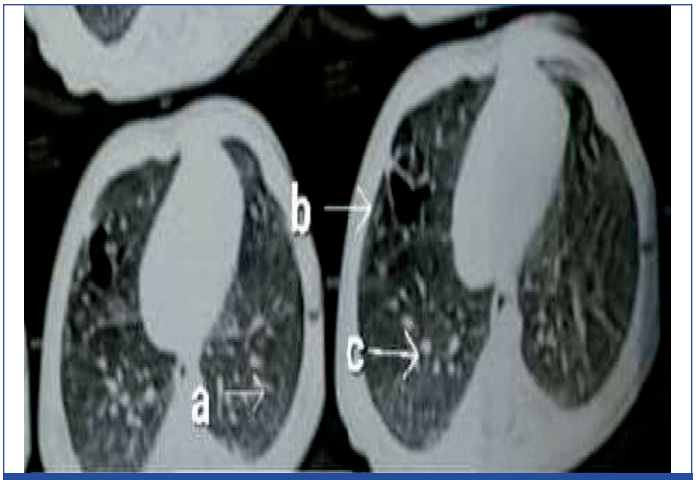
Initial management was focused on supportive care for pneumonia, which included High-Flow Nasal Cannula (HFNC) 6-8 L/min, intravenous antibiotics (Inj. Meropenem @ 40 mg/kg/dose three times daily by infusion over three hours for seven days, Inj. Vancomycin @ 50 mg/kg/day in three divided doses in infusion over one hour for seven days), nebulisation with bronchodilators and hypertonic saline. After transient improvement, the infant deteriorated due to worsening pneumonia. Repeat Chest X-ray showed increased infiltrates. Further evaluation included multiplex Polymerase Chain Reaction (PCR) pneumonia panel, high resolution computed tomography chest and echocardiography.



[Table/Fig-4]: Chest X-ray: a) Diffuse infiltrates bilateral lung fields; b) Absent thymus shadow.

The Computed Tomography (CT) scan confirmed thymic absence and showed diffuse ground-glass opacities, along with small discrete areas of nodular consolidation in both lungs and a few cystic lesions in the right middle lobe [Table/Fig-5]. Echocardiography was normal. Multiplex-PCR revealed three concurrent infections with multidrug-resistant strains of *Pseudomonas aeruginosa*, *Serratia marcescens* and Rhinovirus infection. Ventilator support was advised, but attendants refused; hence, HFNC with increased flow was continued. Therapy was upgraded to Polymyxin (@20, 000 units/kg/days in two divided doses for 14 days) and Ceftazidime-avibactam (@ ceftazidime 150 mg/kg/day in three divided doses and avibactam @25 mg/kg/day in three divided doses for 14 days), resulting in clinical improvement. Immunophenotyping revealed absent T and NK cells, with normal B cells, consistent with X-linked Severe Combined Immunodeficiency (SCID) linked to gene deletion of IL2RG [Table/Fig-6]. WES identified a pathogenic hemizygous missense variant (c.594+5G>A) in the IL2RG gene, likely pathogenic heterozygous Frameshift variant c.6742_6743delAA in Spectrin Beta gene (SPTB gene) and a variant of uncertain significance heterozygous missense variant c.3758A>G in Ankyrin1 (ANK1) gene [Table/Fig-7].

The infant was discharged after 21 days on oral penicillin (@ 125 mg twice daily), fluconazole (@3 mg/kg/day) and folic acid (0.5 mg per day) for one month. He was followed up for one month post-discharge, during which he did not require blood transfusion. The child was referred for Haematopoietic Stem Cell Transplantation (HSCT), but due to financial constraints, it could not be done. The infant succumbed to his illness at 10 months of age during a second episode of pneumonia and severe anaemia requiring blood



[Table/Fig-5]: Computed Tomography (CT) Scan chest: a) ground glass opacities; b) cystic lesions, biggest cystic lesion measuring 14 mm × 6 mm; c) nodular infiltrate.

Immune parameters	Marker	Patient value	Normal Reference Range
Total T lymphocyte	CD3+	480 cells/mm^3	1600-5600 cells/mm^3
Helper T cells	CD3+,CD4+	170 cells/mm^3	1000-4000 cells/mm^3
Cytotoxic T cells	CD3+,CD8+	83 cells/mm^3	400-1700 cells/mm^3
Total B lymphocytes	CD19+	600 cells/mm^3	400-2000 cells/mm^3
Mature B cells	CD20+	350 cells/mm^3	300-1300 cells/mm^3
Natural killer cells	CD16+	Absent	100-1000 cells/mm
	CD56+	Absent	
Serum IgG	-	430mg/dL	200-700 mg/dL
Serum IgM	-	210mg/dL	40-200 mg/dL
Serum IgA	-	44mg/dL	44-840 mg/dL
Patient Immunophenotypic classification	T-B+NK-	X-linked SCID (IL2RG deficiency)	

[Table/Fig-6]: Immunophenotyping and Immunoglobulin profile of the patient. SCID (severe combined immunodeficiency syndrome), IL2RG (Interleukin 2 Receptor gamma)

Gene and transcript	Variant	Location	Zygosity	In silico Parameters	Disorder (OMIM)	Inheritance	Variant Classification
IL2RG NM_000206.3	c.594+5G>A	Exon 4	Hemizygous	CADD: 26.1	Combined immunodeficiency, X-linked; CIDX:312863 severe combined immunodeficiency, X- linked; SCIDX1:300400	X-linked recessive	Pathogenic
SPTB NM_001355436.2	c.6742_6743delAA p.Asn2248fs9	Exon 34	Heterozygous	-	Spherocytosis, TYPE 2; SPH2:616649	Autosomal dominant	likely pathogenic
ANK1 NM_000037.4	c.3758A>G p.Glu1253Gly	Exon 31	Heterozygous	CADD: 29.1 SIFT: Deleterious MT: Damaging	Spherocytosis, TYPE 1; SPH1:182900	Autosomal Dominant Autosomal Recessive	Uncertain Significance

[Table/Fig-7]: Whole Exome Sequencing (WES) showing identified variants.

transfusion. The parents were advised to undergo segregation analysis and genetic counselling.

DISCUSSION

Severe combined immunodeficiency disorder, also referred to as "bubble boy disease", is a condition that severely compromises the immune system [1]. X-linked SCID results from mutations in the IL2RG gene, which encodes the gamma subunit of the IL2R resulting in absent T and NK cells while typically preserving B cell function [2]. Newborn Screening (NBS) in the US has identified an incidence of 1:58,000, while studies suggest similar prevalence rates in India; nationwide data remains limited [3,4].

The field of PIDs in India is largely underexplored, hampered by limited awareness [5]. To the best of our knowledge, this is the first reported case of X-linked SCID associated with HS.

Prior literature documents cases of X-linked SCID associated with hepatoblastoma and disseminated Bacillus Calmette-Guérin disease [6,7]. SCID typically presents in early infancy with recurrent infections, failure to thrive and carries high fatality rates if untreated with HSCT or gene therapy. Atypical presentations may include late-onset symptoms, opportunistic infections or Epstein-Barr virus-related lymphoproliferative conditions [8].

The HS is a common inherited haemolytic anaemia characterised clinically by anaemia, jaundice, and splenomegaly with variable severity. It occurs in all ethnic groups of the world, with the highest frequency of 1:5000 found in northern European countries [9]. The primary cause is the loss of membrane surface area, leading to reduced deformability due to defects in the membrane proteins Ankyrin 1, band 3, β-spectrin, α-spectrin, and protein 4.2 [10].

The patient was co-afflicted with X-linked SCID and autosomal dominant HS, highlighting the complexities of inheritance patterns. Advancements in diagnostic tools, like WES, have revolutionised the diagnosis of SCID [11,12]. Interestingly, the variants reported for all three genes were novel as per Genome Aggregation Database (gnomAD), but reported in ClinVar, which supports the pathogenicity of identified variants. Parental segregation analysis is recommended to confirm the significance of the identified variants further. Diagnostic innovations in NBS for SCID have highlighted the potential for early detection and intervention, which could alter the grim prognosis historically associated with this condition. Since the introduction of the T-Cell Receptor Excision Circle (TREC) assay, many countries have adopted screening for SCID in their NBS [13].

The HS is screened using the osmotic fragility test and HS index (MCHC/MCV ratio >0.36), though both have limited sensitivity. The eosin-5'-maleimide (EMA) dye binding test is now preferred due to high sensitivity (90-95%). Ektacytometry provides functional assessment of red cell deformability, while Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) test identifies specific membrane protein defects [10]. Genetic testing is confirmatory [14].

Management of SCID includes prophylactic antibiotics, immunoglobulin replacement, and definitive treatment like HSCT or emerging gene therapies (such as lentiviral vector-mediated gene addition [15,16]. In Adenosine Deaminase (ADA) deficient patients, enzyme replacement therapy with Pegylated ADA (PEG-ADA) provides interim immune support until definitive therapy.

CONCLUSION(S)

The present case highlights that severe or persistent infections in infancy, with a family history of unexplained childhood deaths, should raise suspicion of SCID, where a detailed family history is key to diagnosis. Consider comprehensive genetic testing for SCID-associated genes IL2RG, ADA, Janus Kinase 3 (JAK3), Recombination-activating genes (RAG1 and RAG2) for accurate diagnosis and precision medicine. The accompanying variants in the SPTB and ANK1 genes underscore the need to consider comorbid conditions. TREC-based PCR assays on dried blood samples are recommended for NBS to enable early SCID diagnosis for better outcomes.

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