Case Report

A case report of severe combined immunodeficiency: Masquerading as sepsis

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ABSTRACT

Severe combined immunodeficiency (SCID) is a rare genetic disorder caused by diverse genetic mutations which lead to the absence or defective T cell, B cell, and Natural killer cell functions. It is usually present in the first 6 months of life and is caused by 20 different mutations. SCID defined by their cellular phenotypes such as T-B+NK+, T-B-NK-, T-B+NK-, and T-B-NK+. Various manifestations are sepsis, disseminated tuberculosis following the Bacillus Calmette–Guerin vaccine, candidiasis, Pneumocystis carinii pneumonia, severe viral infections, chronic diarrhea, failure to thrive, and malabsorption. We report a case of T-B+NK- SCID in a 5-month-old male child, who presented with fever, rash, and loose stool, and the diagnosis was confirmed by whole-exome sequencing.

Key words: Genetic disorder, Severe combined immunodeficiency, Whole-exome sequencing

Severe combined immunodeficiency (SCID) is usually an autosomally recessive inherited primary immunodeficiency disease which typically occurs in infancy [1]. However, 80% of cases are sporadic in occurrence [2]. Infants with SCID are highly susceptible to severe infections [3]. Diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections are the common manifestation. Opportunistic infections such as pneumocystis carinii, candida, and cytomegalovirus are potential threats. It is a true pediatric emergency as death usually occurs by 2 years if untreated. Hematopoietic stem cell transplant and gene therapy are life-saving [4]. A newborn screening test helps to find out the disease even before the symptoms appear ensuring the affected infants receive life-saving treatments [5]. Here, we report a 5-month-old boy who presented with sepsis but had underlying SCID.

CASE PRESENTATION

A 5-month-old male child came to our triage with fever for 10 days, rash for 3 days, loose stool for 1 day, and had no history of cough, cold, vomiting, decreased oral intake, or lethargy. He was admitted to a local hospital on day 3 of illness with fever for 3 days. As fever persisted and inflammatory markers such as C-reactive protein (CRP), ferritin, and D-dimer showed an increasing trend, the child was referred to our center.

The child was first born, from second-degree consanguineous marriage, delivered at term by cesarean section with a birth weight of 3.59 kg. Postnatally, he had a seizure on day 2 of life due to hypocalcemia. Subsequently, he had been well till this illness. On examination, there was some pallor, massive hepatosplenomegaly, and papular rash involving the abdomen, thighs, and perianal region (Fig. 1). The child was admitted as a case of fever with a rash with hepatosplenomegaly with high inflammatory markers with a differential diagnosis of viral exanthem with secondary bacterial infection, Rickettsial infection, multisystem inflammatory syndrome in children (MIS-C), and hematological malignancy.

Reverse transcription polymerase chain reaction for SARS-CoV-2 and COVID immunoglobulin (Ig)G antibodies was negative. However, the parent's COVID IgG was positive though there was no recent or past family history of COVID. Serology for scrub typhus and dengue were also negative (Table 1). Due to the above clinical and laboratory picture, MIS-C with atypical Kawasaki was suspected. Pediatric rheumatologist and cardiologist opinion was taken following which aspirin and IVIG were added. An echocardiogram done showed normal function and coronaries to the extent visualized. Blood and urine cultures showed no growth.

In the next 3 days, rash and fever persisted, pallor increased with the appearance of generalized edema. Hemoglobin dropped from 10.7 to 6.5 g/dL. CRP, ferritin, and D-dimer increased significantly (Table 2). Antibiotic coverage was upgraded to Inj Meropenem and Inj Teicoplanin. Bone marrow aspiration and biopsy were done for hemophagocytic lymphohistiocytosis (HLH) and showed normocellular marrow with myeloid preponderance

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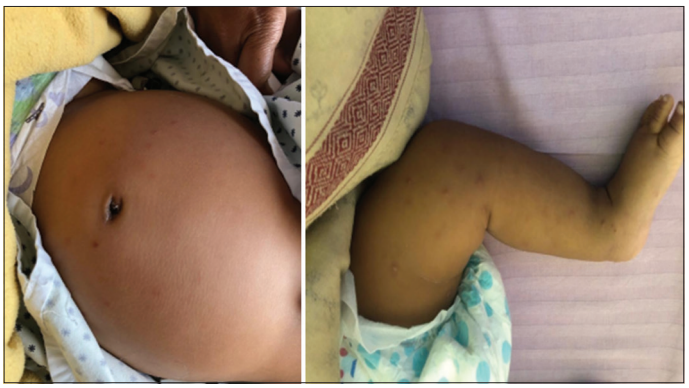

Figure 1: Papular eruptions on abdomen and legs, few on soles with no vesicles

Table 1: Investigation on the day 1

CBC		CRP	110(0-6)
HB	10.7(11-14)	ESR	42(0-10)
PLATELET	3.9lakh(1.5-4.5)	LDH	299(120-246)
TLC	8.6(6-18)	NT PRO BNP	1260(450)
RBC	4.35(4-5.5)	D DIMER	4598(<250)
DC	N86 L12 M5.2	COVID IgG ANTIBODY	NEGATIVE
MCV	76	TRUNAT	NEGATIVE
MCH	24	FERRITIN	819(5-87)
MCHC	32		

- Urine Routine – Normal
- Scrub Typhus- Negative
- Peripheral Blood Smear- Microcytic Hypochromic Anemia with mild Neutrophilia

with scattered HLH activity. Inj Dexamethasone was started for the same. Whole-exome sequencing was sent for familial HLH (Fig. 2).

After a week of hospitalization, fever, rash, and pallor persisted. Ascites increased out of proportion to generalized edema and the child now was irritable with decreased direct breastfeeding. Computed tomography (CT) abdomen was done which showed hepatomegaly, spleen with diffuse hypoattenuation, and gross ascites (Fig. 3). Abdominal paracentesis showed ascitic fluid to be transudative in nature (Cells – 150/L 98%, glucose – 99, albumin – 1.2 g/dl, protein – 2.4, and LDH – 990). On day 9 of hospitalization, the child's neurological issues worsened with the drop in GCS (E2M4V4), pupils dilated but reactive, hypotonia, diminished limb movements, but deep tendon reflexes were elicitable with extensor plantar response. Liver functions were gradually deranged with hyperammonemia (Serum ammonia – 147) and a deranged coagulation profile. Central nervous system HLH was one of the differential diagnoses for the deterioration along with sepsis. Magnetic resonance imaging brain done showed T2 flair hyperintensity in the bilateral dentate nucleus and anterolateral part of bilateral thalami with no diffusion restriction and no contrast enhancement. Electroencephalogram showed diffuse slowing with no PLEDS or electrographic seizures. Lumbar puncture was deferred in view of the deranged coagulation profile.

Table 2: Laboratory investigations

Investigation	1/11	4/11	6/11	8/11	9/11	10/11	11/11
HB (g/dl)	10.7	11.3	6.5	6.2	10	11.6	11.9
TLC (/ul)	8650	5000	6000	6700		9700	
DC (/ul)	N86 L12	N88 L7.3	N97 L0.7	N92 L4.9		N91 L7.5	
Platelets (ul)	3.9L	1.8L	90000	60000	50000	20000	30000
Prothrombin time (sec)					20.5	120	
INR					1.97	11	
Bili (T) (mg/dl)	0.47		0.3			6.3	
Bili (D) (mg/dl)	0.27		0.18			4.8	
Albumin (gm/dl)	3.06		1.6	1.9	2.2	2.0	
SGOT (u/l)	116.4		247		453	1562	
SGPT (u/l)	64		44		97	267	
Creat (mg/dl)	0.3		0.37	0.44	0.26	0.21	
BUN (mg/dl)	19		15		24	13	
Uric acid	3		3.3			3.9	
Na (mmol/l)	134		136		148	149	148
K (mmol/l)	3.9		4		4.6	5.2	4.5
Hco3- (mmol/l)	20					18	
ESR (mm/hr)	42		74				
D-dimer (ng/ml)	4598	5991	5890				
Ferritin (ng/ml)	819	900	11500			18600	
Fibrinogen (mg/dl)			212				
Triglycerides (mg/dl)			151				
LDH (u/l)	299						
NTproBNP (pg/ml)	1260						
Ammonia (umol/l)						147	

HB: Hemoglobin, TLC: Total leucocyte counts, DC: Differential count, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase

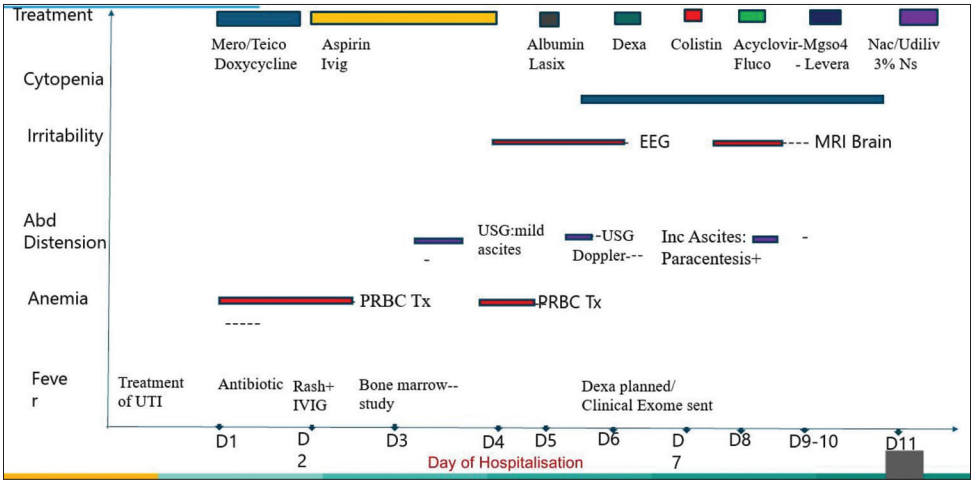

Figure 2: Case management during hospital stay

Subsequently, the child continued to be encephalopathic, persistent massive hepatosplenomegaly, worsening liver failure, progressive pancytopenia, anasarca, skin rash, and fever. In view of the guarded prognosis, parents took the child home against medical advice and the child succumbed in 2 days. After 2 months, the whole-exome sequencing report showed a homozygous mutation of JAK3+ which was suggestive of SCID. It is a missense mutation in exon 16 of JAK3 in chromosome 19 that results in amino acid substitution of isoleucine for methionine at codon 760 resulting in autosomal recessive SCID. Parents were called back and Sanger sequencing done revealed both parents had a heterozygous mutation in JAK3 at exon 16. They have undergone genetic counseling.

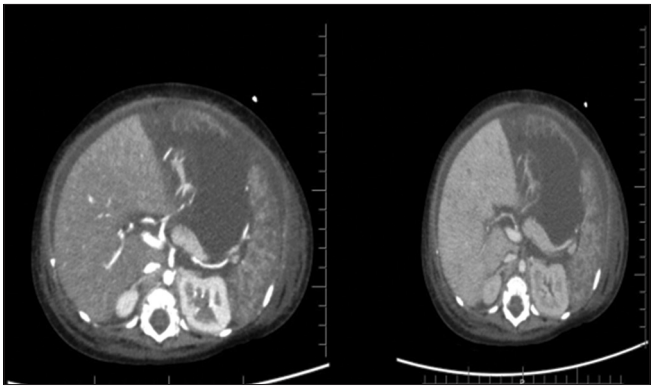

Figure 3: Computed tomography abdomen reveals enlarged spleen with splenic microinfarct and gross ascites

DISCUSSION

SCID was first reported by Glanzmann in 1950 [6] and it is rarely reported in India [7]. It is a rare genetic disorder with a prevalence of approximately 1:50,000 live births [8,9]. The disease is characterized by severe lymphopenia with low count and function of T, B, and NK cells [10]. It is classified as T-B+NK+, T-B-NK-, T-B+NK-, and T-B-NK+ depending on T, B and NK cell functionality.

At present, at least 20 known different genes causing SCID have been identified. Deficiency of common gamma chain T-cell receptor, deficiency of recombinase activating gene 1 and 2, deficiency adenosine deaminase, and deficiency of JAK3 is common among those. T-B+ NK- variety is usually the commonest and X-linked [11].

Children remain asymptomatic at birth, but symptoms start to appear in infancy in the form of frequent episodes of diarrhea, pneumonia, and sepsis. Failure to thrive is common. Common viral and fungal infections are Varicella, Measles, Parainfluenzae, CMV, Epstein Barr, Candida, and Pneumocystis Carinii [12]. It can be screened through newborn screening using the dried blood spot and measuring levels of T-cell receptor excision circles (TREC) [1]. If TREC levels are low; then, a combination of additional tests may be needed to confirm the diagnosis [13].

The best treatment for SCID is stem cell transplantation from the matched related donor and it should be done by 3 months of age. Aggressive treatment of infections is very essential to prevent mortality. Gene therapy if a bone marrow transplant is not possible. Transplantation of stem cells is the only cure currently [14].

In a case series from Wadia, [15] most patients with SCID have persistent lymphopenia (<1500/mm^3), while CD3+T lymphocyte count <500 and hypogammaglobulinemia were seen in 2 of their patients. They all presented with recurrent diarrhea and pneumonia and failure to thrive.

In a study by Aluri *et al*. [16], the majority of patients of SCID presented at 6 months of age similar to our patient. However, in their study recurrent pneumonia (66%), failure to thrive (60%), chronic diarrhea (35%), gastrointestinal infection (21%), and oral candidiasis (21%) were the common presentations, while the index case presented with sepsis. In their study, 21% of patients presented like our case. In another study that looked at molecular features of SCID, of the 254 children who had SCID, 15 (5.9%) had JAK-3 mutation [17].

The child was asymptomatic till 5 months then started presentation as pyrexia of unknown origin. Throughout hospitalization, the child deteriorated gradually with rational antibiotic cover with raised inflammatory markers, progressive cytopenia, and hepatosplenomegaly with deranged LFT. Due to the above picture, HLH was the first d/d along with other

differentials of severe sepsis, resistant fungal and viral infection, and primary immunodeficiency disorders. However, if we think back retrospectively child that was having absolute lymphopenia, we could have done lymphocyte subset and immunoglobulin panel.

CONCLUSION

Key feature of SCID is persistent low lymphocyte count. Combination opportunistic infection and low lymphocyte count are an indication to suspect and proceed toward SCID. Take home points from this case would be to think for an underlying cause of severe sepsis in infants and work up for immunodeficiency if any soft pointers are present.

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