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Case Report

Genetics Section

Concurrent Variants in *SLC29A3* and *EFL1* Genes Presenting as Infantile Onset Transfusion-dependent Anaemia in a Child: A Case Report

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ABSTRACT

Histiocytosis-Lymphadenopathy Plus Syndrome (HLPS) and Shwachman-Diamond Syndrome (SDS) are both rare genetic disorders that primarily affect paediatric patients and present with a wide range of systemic manifestations. HLPS, an autosomal recessive disorder caused by mutations in the *SLC29A3* gene, is characterised by histiocytosis, chronic systemic inflammation, lymphadenopathy, hearing loss and haematological abnormalities. It belongs to a group of inherited histiocytosis syndromes associated with immune dysregulation, leading to recurrent infections and organ dysfunction. SDS, on the other hand, is a congenital bone marrow failure syndrome typically caused by mutations in either the *SBDS*, *DNAJC21*, or *EFL1* genes. It is primarily characterised by exocrine pancreatic insufficiency, skeletal anomalies and varying degrees of cytopenias, particularly neutropenia. Patients with SDS are at an increased risk of developing Myelodysplastic Syndromes (MDS) and leukaemia. The haematological abnormalities in SDS can lead to recurrent infections, anaemia and thrombocytopenia, further complicating its clinical presentation. Present case is of a two-year-old child with transfusion-dependent anaemia, wherein whole exome sequencing identified a pathogenic homozygous variant in the *SLC29A3* gene and a novel homozygous variant of uncertain significance in the *EFL1* gene, which is likely modifying the phenotype. Although *SLC29A3* and *EFL1* gene-related disorders share some haematological and immunological features, their co-existence in a single patient has not been previously reported in the medical literature. Given the complexity of their overlapping manifestations, diagnosing such a case requires comprehensive clinical evaluation and genetic testing. Understanding the interplay between these two conditions can provide valuable insights into their pathophysiology and contribute to improved diagnostic and therapeutic interventions.

Keywords: Genetic disorders, Histiocytosis-lymphadenopathy plus syndrome, Multidisciplinary management, Paediatric anaemia, Shwachman-diamond syndrome

CASE REPORT

The girl, currently two years old, was born to a third-degree consanguineous marriage, at term via normal vaginal delivery, with a birth weight of 2.6 kg and no Neonatal Intensive Care Unit (NICU) admission. She had normal developmental milestones until three months of age when she presented with fever, cold, cough, refusal to feed, pallor, hepatomegaly (3 cm below the right costal margin) and a spleen just palpable. She was diagnosed with bicytopenia, with a haemoglobin level of 1.6 g/dL, total Red Blood Cell (RBC) count of 0.54 million/cmm (normal range: 3 to 5 million/cmm), mean corpuscular volume of 89 fL (normal range: 75-110 fL), mean corpuscular haemoglobin of 30 pg (normal range: 25-35 pg), red cell distribution width of 17.70 (normal range: 11-16), a total white blood cell count of 19,930/cmm (normal range: 6,000-17,000, consisting of 23% neutrophils, 72% lymphocytes, 1% eosinophils, and 4% monocytes), and a platelet count of 28,000/cmm (normal range: 150,000-450,000/cmm). The mean platelet volume was 10.90 fL (normal range: 6-11 fL), and platelet distribution width was 17.30. A peripheral blood smear showed 2-3 schistocytes per high power field, polychromasia, basophilic stippling, target cells, normal white blood cells and giant platelets. Serum Glutamic Oxaloacetic Transaminase (SGOT) was 225 IU/L and Serum Glutamic Pyruvic Transaminase (SGPT) was 376.5 IU/L (both elevated). C-reactive protein was elevated at 22 mg/L (normal is less than 6 mg/L). Urine examination showed glucose 2+, ketones 1+, and blood 3+. Venous blood gas analysis indicated metabolic acidosis. Activated partial thromboplastin time was shortened to 5.55 seconds (control: 26 seconds; normal range: 23-33 seconds). She required Packed Red Blood Cell (PRBC) transfusions, ventilation, and oxygen therapy. [Table/Fig-1] shows the details.

The findings of the bone marrow biopsy performed at three months of age were noted as follows: The bone marrow spaces were very small and located subcortically. There was virtually no erythropoiesis, with erythroblasts present alone and without colony formation. Granulopoiesis was left-shifted and depressed. There were no megakaryocytes; however, there were platelet clots observed on CD61 staining. There was no increase in blasts. The main cell type in the bone marrow was the histiocyte,

Age in months →	3	3.1	7	10	12	15	18	21	22	23	24	25	27	32	40	40.5
Hb (g/dL)	1.6	12.1	7.6	8	6.1	9.5	4.8	7.6	8.3	7.1	14.5	9.8	5.5	7.4	8.1	5.3
RBC (mill/cumm)	0.54	4	2.83	3.5	2.24	3.55	1.98	10.83	2.84	2.48	4.6	3.11	1.79	2.63	3.54	2.32
PCV (%)	4.8	34	23.2	24.9	18.7	29.3	16.9	23.2	25	22.1	42.3	28.4	16.4	24.6	25.1	16.3
TLC (/cmm)	19930	11200	10830	15540	14980	11940	12000	10830	22320	27,290	15,800	11,700	13780	14300	11130	10900
MCV (fL)	89	85	81.8	71.1	83.6	82.4	85.35	81.8	88.1	89.1	92	91.3	91.8	93.54	71	70.3
MCHC (g/dL)	33	36	32.9	31.9	32.7	32.5	28.4	32.9	33.3	32.4	34.2	34.4	33.6	30.8	32.5	32.7

MCH (pg)	30	30	26.9	22.7	27.3	26.8	24.24	26.9	29.4	28.8	31.5	31.4	30.8	28.14	23	23
Platelets (Lac/cumm)	0.97	0.28	2.53	2.51	5.39	3.64	2.54	2.53	3.58	3.81	1.71	4.22	3.54	2.17	3.12	2.57
RDW (%)	17.7	13.6	14.5	17.5	15.3	14.8	15.8	14.5	16.6	14.8	18.9	17.7	17.2	17.4	28	27.8

[Table/Fig-1]: Showing haematological parameters at different age.
Hb: Haemoglobin; RBC: Red blood cells; PCV: Packed cell volume; TLC: Total leukocyte count; MCV: Mean corpuscular volume; MCHC: Mean corpuscular haemoglobin concentration; MCH: Mean corpuscular haemoglobin; RDW: Red cell distribution width

which was of the non langerhans cell type. Phagocytosis was not present, and marrow iron was absent. The serum ferritin was elevated at 3317 micrograms/L (normal range: 21-200). Blood parvovirus Polymerase Chain Reaction (PCR) was negative. Serum erythropoietin levels were greater than 750 mIU/mL (normal range: 4.3 to 29).

An abdominal ultrasound suggested bilateral bulky echogenic kidneys and mild hepatomegaly, with a few irregular hypoechoic areas seen within the spleen. The haemoglobin variant analysis ruled out thalassaemia (HbF 22.3%, HbA 22.2%, HbA1 75.5%), and parental haemoglobin variant analysis was also normal, ruling out beta thalassaemia trait status. Plasma ADAMTS13 activity was normal at 129% (normal range: 50-150%).

Two-dimensional echocardiography at three months of age showed a small to moderate-sized multifenestrated (3.5 mm to 4 mm) atrial septal defect with a left-to-right shunt, trivial tricuspid regurgitation and mild left ventricular hypertrophy. Whole exome sequencing revealed the following findings: The *SLC29A3* gene showed a homozygous variant in exon 4 with the coordinates of chr10:71351578 C>T (GRCh38 format) or c.400C>T (NM_018344.6 transcript ID) or dbSNP ID (vs1430557607) or p.Arg134Cys (missense, arginine to cysteine). This variant can be classified as likely pathogenic according to the American College of Medical Genetics (ACMG) criteria (PM2, PM3, PM5, PP3, PP5), and it is a known pathogenic variant.

The *EFL1* gene showed a homozygous variant in exon 18 with coordinates chr15:82152028 T>C (GRCh38 format) or c.2426A>G or p.Gln809Arg or NM_024580.6 (transcript ID) or rs538304453 (dbSNP ID). The variant in the *EFL1* gene is classified as a variant of uncertain significance, satisfying the following ACMG criteria for pathogenicity: PM2 and BP4. Parental testing was advised.

At seven months of age, she continued to have anaemia and required repeated blood transfusions; however, both platelets and white blood cells were normal. Multidetector Computed Tomography (CT) of the abdomen and pelvis suggested nodular, heterogeneously enhancing splenic parenchyma with capsular and linear parenchymal calcifications-changes that can be seen in splenic changes related to histiocytosis-and a few mildly enlarged lymph nodes at the splenic hilum and right lumbar region. Successive bone marrow studies performed at one and two years post-transfusion were unremarkable. Serum amylase measured at one year was 79 IU/L (normal range: 28-100), and serum triglycerides were 208 mg/dL (normal <150 mg/dL). Bone marrow biopsy done at one year showed marked suppression of the erythroid and myeloid series, with essentially unremarkable megakaryopoiesis. There was no increase in blasts on screening with CD34 and C-kit immunostains. There were no granulomas. A few singly scattered histiocytes were seen on screening with CD68 immunostain. There was no histiocytosis. Haematogones expressing TdT, CD10, and CD20 were noted.

Lymphocyte subset analysis at 1 year 2 months of age showed the following: total white blood cell count 12,060/cmm (normal 5,000-15,000), absolute lymphocyte count 7,863/cmm (65.2%) (normal 3,600-8,900), absolute B lymphocytes (CD3-, CD19+) 1,258/cmm (16%) (normal 720-2,600 or 16.3-26.8%), absolute T lymphocytes (CD3+/CD19-) 5,819/cmm (74%) (normal 2,100-6,200), absolute Th lymphocytes (CD3+/CD4+) 2,988/cmm (38%) (normal 1,300-3,400), absolute Tc lymphocytes (CD3+/CD8+) 2,280/cmm (29%) (normal 620-2,000) (mildly elevated), and absolute natural killer cells (CD3-/CD16+/CD56+) 708/cmm (9%) (normal 180-920).

Serum IgG at one year was 2,221 mg/dL (normal 317-994), IgM was 108 mg/dL (normal 19-146), and IgA was 380 mg/dL (normal 20-100). HBsAg, anti-HCV antibody, HIV p24 antigen, and antibodies to HIV types 1 and 2 were negative. The patient was started on mycophenolate mofetil at 500 mg/m^2/day and steroids for four weeks, considering the diagnosis of pure red cell aplasia. However, this had no effect on anaemia, and the patient continued to be transfusion-dependent.

At 2.5 years of age, the child was admitted to the Paediatric ICU (PICU) due to febrile seizures and status epilepticus. Magnetic Resonance Imaging (MRI) findings indicated diffusion restriction in the white matter of the left centrum semiovale, along with an acute non haemorrhagic infarct and parietal ischaemia. The Electroencephalogram (EEG) was normal. At present, the baby had persistent hypertensive readings, which were initially noted, leading to the involvement of paediatric nephrology. A renal Doppler study was performed, which was normal. The child was evaluated for Brainstem Evoked Response Audiometry (BERA), which was also normal.

Behaviour studies were conducted at three years and 10 months, and according to the Vineland Social Maturity Scale (VSMS), the social age was three years and 10 months, with a Social Quotient (SQ) of 100 indicating average social functioning. At present, clinically, the patient is having normal growth, with a height of 95 cm (between the 3rd and 50th percentiles) and a weight of 13.5 kg (between the 3rd and 50th percentiles). Upon examination, the child was found to have mild hepatosplenomegaly, with no other physical examination findings as seen in [Table/Fig-2]. Current treatment includes monthly

[Table/Fig-2]: Physical examination- normal findings.

blood transfusions for anaemia, oral iron chelators, supportive care with antiepileptic and antihypertensive medications, and long-term follow-up for persistent hypertension.

DISCUSSION

HLPS and SDS are both rare genetic disorders with overlapping haematological manifestations [1,2]. HLPS, caused by mutations in the *SLC29A3* gene, is characterised by histiocytosis, chronic systemic inflammation and multisystem involvement, including skin hyperpigmentation, lymphadenopathy and hearing loss [3,4]. SDS, primarily associated with mutations in SBDS, DNAJC21, or *EFL1*, manifests as bone marrow failure, pancreatic insufficiency, and skeletal abnormalities [5]. The primary diagnosis in present case was *SLC29A3*-related histiocytosis, as the identified p.Arg134Cys variant is a known pathogenic mutation frequently reported in the Indian population [6-9]. Unlike typical HLPS cases, index patient did not exhibit hallmark extra-haematological features such as skin hyperpigmentation, hypertrichosis, or endocrinopathies at presentation, although these may emerge later in life. The patient's haematological abnormalities, including transient histiocytosis in the bone marrow, align with prior HLPS reports. However, the co-occurrence of an *EFL1* gene variant introduces diagnostic complexity. The role of the *EFL1* gene variant in this patient remains uncertain. *EFL1* mutations are known to contribute to SDS through defective ribosome biogenesis, leading to haematopoietic dysfunction [5]. However, index patient lacked classical SDS features, such as pancreatic insufficiency, skeletal dysplasia, or chronic neutropenia. Given this, the *EFL1* variant in this case could represent a hypomorphic (weakly pathogenic) or likely benign variant rather than a causative mutation.

Interestingly, previous reports have documented pure red cell aplasia in patients with *SLC29A3* mutations, which may explain the patient's transient bone marrow findings [10]. Additionally, persistent hypertension and ischaemic brain injury, as observed in index patient, are atypical for both HLPS and SDS, warranting further investigation into potential modifying genetic or environmental factors.

Given the rarity of HLPS and its potential for progressive multiorgan involvement, long-term follow-up is essential. While index patient had not yet exhibited classic HLPS-associated extra-haematological features, continued monitoring is warranted, particularly for endocrinopathies, cardiac abnormalities and hearing impairment. The patient has been advised to undergo HLA typing in anticipation of a potential bone marrow transplant, which remains the definitive treatment for severe haematological involvement in HLPS.

Targeted therapeutic approaches, such as IL-6 receptor blockade (e.g., Tocilizumab), have shown efficacy in reducing systemic inflammation in HLPS patients, with reports indicating symptomatic improvement and suggesting a potential future intervention if inflammatory manifestations arise. However, further studies are needed to clarify the role of immune modulation in HLPS management.

Several case reports illustrate the diverse presentations of HLPS and SDS. In HLPS, a 12-year-old female with an *SLC29A3* mutation presented with progressive hand contractures, hyperpigmentation, and hypertrichosis, responding well to Tocilizumab [11]. Another case involved a 9.5-year-old male with systemic inflammation requiring long-term immunosuppressive therapy [12]. SDS cases also exhibit varied clinical features. A Korean child with SDS displayed classic manifestations, including pancreatic insufficiency and skeletal abnormalities [13], while a severe neonatal case demonstrated early-onset neutropenia and pancreatic insufficiency, highlighting the need for early diagnosis and intervention [14]. Additionally, an SDS patient with hepatic cirrhosis underscores the importance of hepatic monitoring, reinforcing the multisystem nature of these disorders [15].

CONCLUSION(S)

The coexistence of HLPS (pathogenic variant) and SDS (mild variant) in a single paediatric patient presents a unique diagnostic and therapeutic challenge. This case highlights the crucial role of genetic testing in unraveling rare disorders with overlapping manifestations. Early identification and a multidisciplinary approach are essential for optimal patient management. Clinicians should consider rare genetic syndromes in cases of unexplained haematological and neurological symptoms, ensuring timely intervention and improved patient outcomes. Continued research and increased awareness of such conditions will enhance diagnostic capabilities and guide future treatment strategies.

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