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CASE REPORT

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A rare case of heme oxygenase deficiency: A case report and literature review

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Key Clinical Message

Heme oxygenase deficiency, a rare condition disrupting heme metabolism, has only nine reported cases. We present a 3-year-old boy with dysmorphic facies, asplenia, and normal bilirubin levels despite ongoing hemolysis. Blood transfusions sustained hemoglobin while IV steroids managed inflammation.

KEYWORDS

asplenia, bilirubin synthesis, heme oxygenase deficiency, HMOX1 gene

1 | INTRODUCTION

Heme oxygenase (HO) is an important enzyme in heme metabolism. It facilitates the conversion of heme to biliverdin, which is further converted to bilirubin. Other products of heme metabolism include free ferrous iron and carbon monoxide (CO). There are three isoforms of this enzyme. HO-1 is an inducible form and is expressed in the reticuloendothelial system in response to hypoxia and ischemia. HO-2 is constitutively expressed in the brain, testis, and vascular endothelium and maintains cellular heme levels. The biological function of HO-3 is presently under investigation. Bilirubin protects cells from oxidative injury by scavenging reactive oxygen species.[1] CO acts as a signaling molecule in vasodilation, anti-inflammatory reactions, and cellular defense against apoptosis and oxidative damage.[2] HO releases free iron, which gets incorporated into ferritin to maintain cellular iron homeostasis.

Several studies have examined the role of HO-1 in in vitro tests and animal models. However, based on

available reports,[3,4] only nine human cases have been documented since its first description by Yachie et al. in 1999. The rarity of this condition may be attributed to the crucial role of HO-1 in fetal growth and development. Reported cases exhibit a wide range of age of onset, from infancy to 15 years. Despite this variation, many similarities have been observed in their clinical presentation and laboratory findings. Most notably, patients typically exhibit abnormally low or normal bilirubin levels despite active hemolysis. Other findings include asplenia, vasculitis, nephritis, and features of hemophagocytic lymphohistiocytosis (HLH).[3] We present a case of a 3-year-old boy with HO 1 deficiency. We aim to focus on the literature review and widen the gaze of clinicians on this rare entity.

2 | CASE HISTORY & EXAMINATION

A 3-year-old boy presented to the pediatrics outpatient department with a complaint of high-grade intermittent fever for 1 week and cough for 3 days. The patient also had a history of four to five episodes/day of non-bilious, non-projectile vomiting and dull activity in the past 1 day. Additionally, the patient had decreased oral intake. The patient also had recurrent episodes of fever in the past, managed with multiple admissions.

The patient was born out of a consanguineous marriage. On examination, he had dysmorphic facies, frontal bossing, a depressed nasal bridge, and large ears. He was febrile (100°F in Southern India), maintaining saturation at room air. The patient had signs of dehydration and also had pallor. On auscultation of the chest, air entry was decreased on the left side, with normal heart sounds and no murmur. The abdomen was soft without organomegaly. Examination of other systems including the spine was normal.

3 | METHODS

The patient was administered IV fluids and IV antibiotics after sending a blood sample for culture. He was treated symptomatically with antipyretics, antiemetics, antihistamines, and antacids. The results of initial blood investigations are presented in Table 1. As the blood culture came negative and the fever subsided antibiotics were de-escalated and the child was started on IV methylprednisolone, given elevated inflammatory markers.

Ultrasonography abdomen revealed a smaller size of the left lobe of the liver and the spleen was not visualized. CT abdomen confirmed asplenia. During the hospital stay, the child had recurrent episodes of vomiting followed by dull activity. Hence the child's vitals monitoring was done, which showed high blood pressure. The patient had an episode of seizure activity and upward rolling of the eyeballs hence was started on IV antiepileptics and anti-hypertensive infusion. However, MRI brain, MR venogram, and EEG did not reveal any significant findings. USG renal Doppler was normal and endocrinological workup was inconclusive for hypertension. As the patient's blood pressure settled, the anti-hypertensive infusion was slowly tapered and stopped and oral antihypertensives were administered.

As the patient was having persistent fever spikes, elevated ferritin, LDH levels, liver enzymes, thrombocytosis,

TABLE 1 Positive laboratory findings in the patient.

Diagnostic Test	Result	Reference Range
Hemoglobin	4.8 g/dL	10.5–13.5 g/dL
Red blood cells	1.79 millions/mm^3	4.1–5.5 millions/mm^3
Platelets	22.05 lakhs/mm^3	1.5–4.5 lakhs/mm^3
White blood cells	59,890 cells/mm^3	4500–13,500 cells/mm^3
Neutrophils	52%	54–62%
Lymphocytes	45%	25–33%
CRP	25 mg/L	<10 mg/L
ESR	70# mm/h	0–10 mm/h
LDH	17,910# μ/L	225–450μ/L
Total bilirubin	0.7 mg/dL	1–1.2 mg/dL
Direct bilirubin	0.2 mg/dL	0.0–0.3 mg/dL
SGOT	348# IU/L	0–45 IU/L
Alkaline phosphatase	395# IU/L	110–310 IU/L

Abbreviations: CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, SGOT: serum glutamic acid oxaloacetate test.

leukocytosis, asplenia, and dysmorphic facies, a multitude of evaluations were performed to rule out various pathologies. Hb electrophoresis was found to be normal and the patient was negative for JAK 2 mutations. Elevated LDH levels, decreased RBC count, and erythroid hyperplasia with normoblastic and megaloblastic maturation on bone marrow aspiration, confirm hemolysis. Low bilirubin levels despite continuous hemolysis raised suspicion about a possible defect in the heme metabolic pathway. Whole exome sequencing detected a pathogenic variant responsible for the reported phenotype. A homozygous nonsense variant in Exon 2 of the *HMOX1* gene (chr22: g.35383212>T; Depth: 84x) that results in a stop codon and premature truncation of the protein at codon 44 (p. Arg44Ter: ENST00000216117.9) was detected (Table 2). The observed variant lies in the "HO" domain of the HMOX1 protein.

4 | CONCLUSION & RESULTS

Hence the patient was diagnosed to be suffering from HO 1 deficiency. The parents were explained about the disease and that it was a rare condition. The patient was administered blood transfusions to maintain hemoglobin and was also started on IV steroids to control inflammation. The patient was stabilized after an inpatient hospital stay of 1 week. He was discharged with advice for a monthly workup and blood transfusion.

5 | DISCUSSION

HMOX1, an inducible enzyme, plays a crucial role in defense against oxidative stress by degrading heme, a strong pro-oxidant causing high oxidative stress in the body, to biliverdin, iron, and CO. These products help in further reducing oxidative stress, endothelial functioning, and iron recycling. The HMOX1 genes are located on chromosome 22q12. A rare autosomal recessive condition called HO-1 deficiency occurs due to a missense or nonsense mutation in these genes. Nine cases of HO deficiency have been reported so far (Table 3).

In HMOX1 deficiency, the response to oxidative stressors is impaired and is characterized by high heme and low bilirubin, ferritin, and CO.[13] This causes uncontrollable cell injury, particularly in the liver, kidneys, monocytes, and endothelium. HMOX1 deficiency causes the continuous death of splenic macrophages due to the inability to detoxify heme. This causes splenic fibrosis and asplenia. In some cases, the spleen initially enlarges postnatally and later atrophies.[3,14] Asplenia was detected in three out of nine case reports, apart from ours.[7,9,12] Macrophage

TABLE 2 Pathogenic variant detected in the patient on genomic analysis.

Gene (transcript)	Location	Variant	Zygosity	Disease	Inheritance	Classification
HMOX1 (+) (ENST00000216117.9)	Exon 2	c.130C>T (p. Arg44Ter)	Homozygous	Heme oxygenase-1 deficiency	Autosomal recessive	Pathogenic (PVS1, PM2, PP5)

TABLE 3 Review of literature on the heme oxygenase deficiency cases reported to date.

First author	Year	Place of study	Age of onset/ diagnosis	Clinical presentation	Investigations	Treatment given	Outcome
Yachie et al.[3]	1998	Japan	26 months	Recurrent fever, generalized erythematous rash, growth retardation, hepatomegaly, asplenia, hematuria, proteinuria	↑ WBC, ↓ RBC, ↓ Hb, ↓ Hct, ↑ LDH, ↑ SGOT, ↑ Ferritin, ↓ Fibrinogen, ↑ Fibrin degradation product, ↑ D-dimer, ↑ Thrombin-antithrombin complex, ↑ Plasmin-α2 plasmin inhibitor complex, ↑ Thrombomodulin, ↑ vWF, Hyperlipidemia, ↑ Triglyceride, ↑ Total cholesterol, ↑ LDL, ↓ Total bilirubin, ↑ Serum haptoglobin concentration, ↑ Serum heme concentration, **Renal biopsy**: mild mesangial proliferation, endothelial detachment from the glomerular basement membrane, thickening of the capillary loop within the glomeruli, scattered lymphocyte infiltration seen **Liver biopsy**: mild inflammatory changes with minimal lymphocyte infiltration **Transmission electron microscopy of kidneys**: endothelial swelling, detachment of glomerular capillary, unidentifiable material was deposited between the detached endothelium and glomerular basement membrane **PBF**: lipid in the upper layer, dark maroon color, microcytic hypochromic RBC, ↑ turbidity, fragmented or dysmorphic bizarre-shaped erythrocytes, Erythroblasts present, Howell-Jolly bodies present, platelets present.	Oral steroid, NSAIDs, erythrocyte	N/A
Ohta et al[5]	2000	Japan	2 years	Recurrent fever, asplenia, hematuria, proteinuria, generalizederythematous rash, growth retardation, hepatomegaly, cervical lymphadenopathy	N-acetyl-b-D-glucosaminidase (NAG) ↑↑, b2-microglobulin ↑↑, ↓ serum bilirubin concentration, ↑↑ Haptoglobin	N/A	N/A
Kawashima et al[6]	2002	Japan	2 years	Recurrent fever, generalized erythematous rash, arthralgia, growth retardation, hepatomegaly, cervical lymphadenopathy, asplenia	↓ Hb, ↑ WBC, ↑ Platelets, ↑ lipids, ↑ haptoglobin, ↑ ferritin, ↑ thrombomodulin, ↑ vWF, ↑ heme, normal bilirubin **DNA analysis**: HMOX-1 gene mutated in both alleles of the patient	Oral steroids, NSAIDS, blood transfusions	Died

TABLE 3 (Continued)

First author	Year	Place of study	Age of onset/ diagnosis	Clinical presentation	Investigations	Treatment given	Outcome
Radhakrishnan et al[7]	2011	India	15 years	High-grade fever, cervical lymphadenopathy, asplenia, hematuria, massive proteinuria, hypertension, bleeding (epistaxis, diffuse alveolar hemorrhages in both lungs, perinephric hematoma), diffuse macular skin rash, seizures, periorbital puffiness	↓ Hb, ↑WBC, ↑Platelets, ↑ LDH, ↑↑Ferritin, ↑ C-reactive protein, ↑ IL-6, ↑ vWF, ↑ D-dimer **CT abdomen**: nonrotation of the gut with the jejunum and ileum in the right hemi-abdomen and asplenia. **LFT**: ↑↑AST, ↑ALT, mild↑ total serum bilirubin **PBF**: RBC agglutination, fragmented cells, spherocytes, normoblasts Positive Direct Coombs, positive cold agglutinins, positive cryoglobulins **Renal biopsy**: normal glomeruli with mild mesangial prominence, little detectable HMOX-1 in renal tubules (immunostaining) **Serum protein electrophoresis**: ↑ alpha-2 band **DNA analysis**: Chromosome 22q12 mutation, absent HMOX-1	Azithromycin, IV methylprednisolone, oral prednisolone, packed cell transfusions, IV cyclophosphamide followed by rituximab, recombinant factor VIIa, peritoneal dialysis.	Died (5 months)
Gupta et al[8]	2015	India	14 months	Recurrent fever, cola-colored urine, proteinuria, microscopic hematuria, mild hepatomegaly, small spleen	↑ WBC, ↑ platelets, ↓ serum bilirubin, ↑ ferritin, ↑ haptoglobin **Urine analysis**: proteinuria, microscopic Haematuria **DNA analysis:** variation in exon 2 of the HMOX1 gene	N/A	Died
Satya Prakash Yadav et al[9]	2018	India	10 years	Fever, pallor, severe hypertension, short stature, abnormal facies with normal development	↓Hb, ↑Platelets, ↑Ferritin, Urine albumin 4+, urine hemoglobin-positive **USG abdomen**: asplenia **DNA analysis**: homozygous missense mutations in exon2 (R44X) on chromosome 22q12	Prednisolone, hydroxyurea, mycophenolate mofetil (MMF), matched sibling donor allogeneic stem cell transplant with non-myeloablative conditioning	Recovered
Tahghighi et al[10]	2019	Iran	17 months	Recurrent fever, tachypnoea, respiratory distress, hepatomegaly	↓ Hb, ↑ WBC, ↑ Platelets, ↑ ESR, ↑ CRP, ↑ LDH, ↑ AST, ↑ ALT, ↑ ALP, ↑ GGT, ↑ Triglycerides, ↑ Cholesterol, ↑ Ferritin, ↑ Creatine phosphokinase, ↓ Fibrinogen, Normal bilirubin **ECHO**: Massive pericardial effusion **Abdominal USG**: Hepatomegaly, normal spleen **Liver biopsy**: Iron deposits **DNA analysis**: Homozygous mutation (exon3: c.A610T, p.K204X) on the HMOX1 gene (parents heterozygous)	IV methylprednisolone, Oral steroids, Ibuprofen, Vancomycin and ceftriaxone, Cotrimoxazole	Died

(Continues)

TABLE 3 (Continued)

First author	Year	Place of study	Age of onset/ diagnosis	Clinical presentation	Investigations	Treatment given	Outcome
Chau et al[11]	2020	USA	4 years	Recurrent fever, fatigue, cough, hepatomegaly, asplenia, hemoglobinuria, growth retardation, arthralgia	↓ Hb, ↑ WBC, ↑ Platelets, ↑ Ferritin, ↑ D-dimer, ↑ TG, ↑ ↑ LDH, ↑ AST, ↓ fibrinogen, normal bilirubin **CT abdomen**: Poorly perfused spleen **PBF**: Howell Jolly Bodies & Schistocytes **Lung Biopsy**: Cholesterol Granulomas and Interstitial pneumonia from repeated flares **BM biopsy**: Hemophagocytic lymphohistiocytosis with normal cellularity. **DNA analysis**: confirmed HMOX-1 deficiency **Western blot analysis**: absence of HMOX-1.	Oral steroids, anakinra, cyclosporine, tocilizumab	Died
Soumya Renji et al[12]	2021	India	8 months	Recurrent Fever, dysmorphic facies, frontal bossing, depressed nasal bridge, large ears, pallor, hepatomegaly, delayed development, growth retardation, auto splenectomy (during treatment), acute arterial stroke	↑ CRP, ↑ Ferritin, ↑ LDH, ↑ AST, ↑ ALT, ↓ Hb, ↓Platelets **BM examination**: hemophagocytes **USG Abdomen**: absent spleen **Hemoglobin electrophoresis**: sickle cell trait **DNA analysis**: revealed homozygous nonsense variation in exon 3 of the HMOX1 gene (OMIM*141250), Sanger sequencing-confirmed HOX-1 deficiency **MRI**: confirmed acute arterial stroke	Oral steroids, blood transfusions	Died (3&1/2 years)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, bone marrow; CRP, C-reactive protein; HMOX, heme oxygenase; LDH, lactate dehydrogenase; LFT, liver function tests; PBF, peripheral blood film; RBC, red blood cell; vWF, Van Willebrand factor; WBC, white blood cell; ESR, erythrocyte sedimentation rate.

dysfunction also impedes iron trafficking from peripheral tissues, causing iron deposition in the liver and kidneys, as reported by Tahghighi et al.[10] Severe hemolytic anemia with elevated heme, Hp-Hb complexes, and low bilirubin ensues.[3] HMOX1 deficiency causes severe systemic inflammation from monocyte dysfunction; abnormal fibrinolysis, coagulation, and DIC due to systemic vascular endothelial injury; renal tubulointerstitial damage; and increased heme-catalyzed LDL oxidation, promoting atherosclerosis.[13] It primarily results in recurrent miscarriages or intrauterine deaths, but due to various genetic and environmental factors, disease presentation can be delayed until a later age.[14]

HO deficiency exhibits diverse clinical manifestations contingent upon the specific enzyme subtype affected. The onset of clinical features demonstrates significant variability, ranging from the neonatal period to 15 years of age. The most commonly seen characteristic facial features are a depressed nasal bridge, a prominent forehead, and significant eyelid edema, as seen in the current case. Other common clinical presentations include hepatomegaly, asplenia, hemolytic anemia, low bilirubin, iron overload, and chronic systemic inflammation. These pathological processes may culminate in pain, fatigue, and recurrent pyrexia. Two studies reported renal impairments such as hematuria and proteinuria as recognized complications associated with HO deficiency.[5,10] However, urine abnormalities were not found in the current case. Rarely, neurological manifestations such as intellectual disability, developmental delays, and seizures may present. Patients with HO deficiency frequently exhibit immunological dysfunction and increased susceptibility to infections. Notably, hypertension, cerebral hemorrhage, and fungal sepsis have been implicated in contributing to mortality. The free Hb released during hemolysis scavenges serum nitric oxide leading to vasoconstriction, which results in hypertension.[3] A partial deficiency in HO-1 increases the progression and mortality of sepsis.[15] A familial history of intrauterine fetal demise and consanguineous marriages is observed in a subset of patients with HO-1 deficiency.[3]

The absence of HMOX-1 can lead to significant sequelae in organ systems across the body. The cases of HMOX-1 deficiency reported so far demonstrated signs of asplenia with signs of leucocytosis and thrombocytosis. In a case reported by Gupta et al., asplenia or hyposplenism along with leucocytosis with thrombocytosis serves as an important clue to diagnosing HMOX-1 deficiency.[8]

Examination of the first autopsy case by Yachie et al. revealed a characteristic tissue injury predominantly in the liver, kidney, vascular endothelial cells, and monocytes in the blood. The kidney showed injuries to the glomerulus along with tubulointerstitial injury with tubular atrophy. Glomerulus under electron microscopy showed mild mesangial proliferation along with capillary loop thickening. The liver demonstrated a massive increase in size due to amyloid accumulation, resulting in hepatocyte atrophy. Iron deposits were present across the liver and kidney. The monocytes showed a central vacuolation and decreased expression of surface antigens.[3] In a case reported by Chau et al., a lung biopsy showed signs of interstitial pneumonia, patchy pleural fibrosis as well as scattered cholesterol granulomas due to repeated flares of hyperinflammation triggered by an infection.[11] Tahghighi et al., reported massive pericardial effusion in a 17-month-old patient diagnosed with HMOX-1 deficiency.[10]

The laboratory data from various cases surprisingly demonstrate uniformity. In each instance, the CBC shows an elevation in leukocyte and platelet count. Urine analysis consistently reveals hematuria and proteinuria in Japanese and Indian cases, indicating potential kidney injury. Interestingly, LFTs demonstrate elevated AST and ALT levels in all cases, yet bilirubin levels persistently remain low or within normal ranges despite the presence of active hemolytic anemia, establishing this as the primary hallmark feature. Additionally, markedly elevated serum ferritin and LDH values serve as a second hallmark. Furthermore, there is inconsistency in the levels of CRP and ESR, some cases exhibit elevated levels, while others display normal levels. A bone marrow biopsy in one of the cases revealed slight hemophagocytosis. Lastly, on ultrasound abdomen or CT abdomen, the absence or hypoplasia of the spleen is a frequent occurrence, although even a normal-sized or enlarged spleen does not rule out HO-1 deficiency.

HO deficiency is diagnosed primarily through a genetic study using techniques such as whole exome, whole genome, and targeted sequencing. Sequence analysis showed that the paternal allele had a 2-nucleotide deletion inside exon 3 and the maternal allele had a full deletion of exon 2.[3] Because consanguinity increases the likelihood of heterozygosity and genetic drift, it also increases the prevalence of HO deficiency. Several cases of HO deficiency have been linked to consanguinity similar to the current case. Among these, a notable case was reported by Tahghighi et al., involving an Iranian boy with HO deficiency, who was born to consanguineous parents.[10] Thus, genetic counseling and screening are crucial for its prevention.

The patient's clinical presentation suggests a potential diagnosis of Ivermark syndrome, a unique variant of heterotaxy characterized by congenital heart defects and abnormal arrangements of internal organs, particularly with right-sided involvement,[16] leading to absent spleen development.[17] Another differential diagnosis to consider is autoimmune polyendocrinopathy candidiasis ectodermal

dystrophy syndrome (APECED), a rare autoimmune disorder caused by mutations in the autoimmune regulator (AIRE) gene.[18] APECED typically presents with hypoparathyroidism, primary adrenal insufficiency (Addison's disease), and chronic mucocutaneous candidiasis (CMC).[18] Additionally, Stormorken syndrome, a rare genetic condition associated with mutations in the stromal interaction molecule 1 (STIM1) gene, may be considered.[19] This syndrome is characterized by thrombocytopenia, asplenia, muscle weakness (myopathy with tubular aggregation), and miosis.[19]

Based on an extensive review of the literature, it is evident that a universally accepted therapeutic protocol for HO deficiency is currently deficient. Clinical management mainly involves administering treatment modified to meet the specific needs of the affected individuals. Particularly, corticosteroids, hydroxyurea, and immunosuppressants such as mycophenolate mofetil, tacrolimus, and blood transfusions have been vital to disease management. Corticosteroids contribute to inflammation reduction, as demonstrated by decreased levels of inflammatory markers in a study conducted by Natalie et al.[20] In addition, various antibiotics, including azithromycin, vancomycin, ceftriaxone, cotrimoxazole, and monoclonal antibodies, such as rituximab and anakinra, were used to modulate the immune response. Other interventions included recombinant factor VIIa, peritoneal dialysis, and packed cell transfusions. There is only one piece of literature supportive of the effectiveness of HLA-matched stem cell transplantation. As such non-myeloablative allogeneic matched sibling donor (MSD) stem cell transplantation emerges as a viable therapeutic avenue for individuals afflicted with autoinflammatory disorder resulting from HO deficiency. Despite its promise, mixed chimerism raises apprehensions about this treatment modality.[9]

The prognosis of the HO deficiency may vary among people. Several factors like the severity of the disease, time of intervention, and effectiveness of the treatment play vital roles in determining the same. The rarity of HO deficiency leads to the availability of limited data, underscoring the need for additional research and larger case studies to understand better the prognosis and ideal management approach for this condition.

AUTHOR CONTRIBUTIONS

Sai Santhosha Mrudula Alla: Conceptualization; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing. **Pahel Agarwal:** Data curation; writing – original draft. **Dhruv J. Shah:** Data curation; writing – original draft. **Waseem Abrar Shajahan:** Data curation; writing – original draft. **Rakshna Ramsundar:** Data curation; writing – original draft. **Deekshitha Alla:** Conceptualization; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing. **Madhavi Ravulapalli:** Data curation; writing – original draft. **Satya Bora:** Data curation; writing – original draft. **Sanjay Pillai:** Data curation; writing – original draft. **Ruth G. Bayeh:** Writing – review and editing. **Uday Kumar Repalle:** Data curation; writing – original draft. **Fnu Suhani:** Data curation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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