Coexistence of Hemoglobin D and Thalassemia Trait: A Rare Phenomenon with Cardiac Presentation

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Abstract

Hemoglobin D (HbD) is a hemoglobin variant predominantly found in the northwestern regions of India, such as Punjab and Gujarat, as well as in Pakistan, Iran, and other countries. This variant results from a genetic mutation at the 121st amino acid residue, where glutamic acid is replaced by glutamine. HbD can occur in either homozygous or heterozygous forms. Individuals with HbD typically remain asymptomatic throughout their lives. Nonetheless, HbD can occasionally coexist with sickle cell disease, leading to clinical manifestations. The co-inheritance of HbD with thalassemia, though rare, is believed to present clinically, though such cases are scarcely documented in the literature.

This article reports a case from the Bathinda district of Punjab involving a patient with coexisting HbD and thalassemia trait who presented with severe cardiac symptoms, potentially as a late consequence of hemoglobinopathy due to underlying chronic anemia. Additionally, we propose an algorithm designed to assist clinicians and diagnostic laboratory experts in the streamlined evaluation of hemoglobinopathies. This is particularly relevant given the limited availability and affordability of genetic allele testing in most clinical settings.

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Introduction

Hemoglobinopathies are rare hematological disorders caused by genetic mutations. Among these, hemoglobin D (HbD) is a hemoglobin variant predominantly found in northwest India, Pakistan, and Iran.[1] HbD differs from normal adult hemoglobin (HbA) at the 121st position of the β chain, where glutamic acid is replaced by glutamine. The most common type of HbD variant is HbD-Punjab, also referred to as HbD-Los Angeles.[2] HbD is a stable variant that can occur in either homozygous or heterozygous forms, and individuals with this variant typically remain asymptomatic throughout their lives.[3]

While HbD can coexist with sickle cell disease, leading to clinical manifestations, its coexistence with thalassemia trait is rare and is believed to present with variable clinical symptoms.[4] Nevertheless, such cases are not extensively documented in the literature.

In this article, we report a case of coexisting HbD and thalassemia trait with a clinical presentation of cardiac symptoms.

Case Report

A 67-year-old man, a retired postman from the state of Punjab, India, experienced a sudden onset of acute dyspnea and profuse sweating. He initially sought relief by taking bronchodilators (a combination of theophylline, etophylline, and a steroid) from a local pharmacist, but his symptoms persisted. Consequently, he was brought to the emergency department of a nearby hospital for further evaluation and management.

Arterial blood gas analysis conducted at the hospital revealed low oxygen saturation (SO_2: 89.59% and pO_2: 71.41 mm Hg). The patient was administered oxygen via nebulization, which provided temporary relief, and he was subsequently discharged. However, over the next 15 days, his dyspnea progressively worsened. He then presented to our hospital's department of cardiology, where he was diagnosed with grade III dyspnea according to the New York Heart Association criteria. The dyspnea was accompanied by orthopnea and paroxysmal nocturnal dyspnea, indicating cardiac involvement. Notably, the dyspnea was not associated with fever.

A physical examination revealed pallor in the patient. Nonetheless, there was no evidence of pedal edema, engorged neck veins, cyanosis, or clubbing of the nails. In addition to dyspnea, the patient reported a history of type 2 diabetes mellitus, for which he had been taking oral hypoglycemic medications (metformin, pioglitazone, and glimepiride). He had also been self-monitoring his blood glucose levels at home using a glucometer to manage his diabetes.

The patient had no chronic history of dyspnea, ruling out conditions such as chronic bronchitis or asthma. There was also no history of past blood transfusions, either for the patient or his family members. Clinically, the patient reported no bladder or bowel-related complaints. Additionally, examinations of the abdomen and nervous system revealed no abnormalities and were within normal limits.

To further evaluate the cardiac system and assess the current status of diabetes control, diagnostic tests were conducted, including ECG, echocardiography, chest X-ray, hematological tests, biochemical cardiac markers, HbA1c, and blood glucose estimation. Additional laboratory tests were performed to rule out systemic involvement in other organs. A surprising finding during these investigations was that the HbA1c level could not be detected by our analyzer, which uses high-performance liquid chromatography (HPLC). This prompted further analysis of hemoglobin fractions, which revealed elevated levels of HbD, moderately increased HbF, and reduced levels of HbA0 and HbA2.

The elevated HbD levels suggested that the patient likely had the HbD-Punjab variant, consistent with his geographic origin in the Bathinda district of Punjab. The findings also indicated the coexistence of a thalassemia trait, presenting with cardiac symptoms, anemia, and occult stool blood loss. All clinical and laboratory findings were compiled and are summarized in Tables 1-6.

The clinical findings are summarized in Table 1. Hematological results and the iron profile are presented in Table 2. Quantitative data on various hemoglobin fractions are detailed in Table 3. The results of biochemical cardiac markers are displayed in Table 4, while the glycemic profile and other biochemical test results are outlined in Table 5 and Table 6. In addition, we have formulated an algorithm to guide the diagnostic workup of suspected hemoglobinopathy cases, which is illustrated in the accompanying figure.

The patient provided consent for the publication of his clinical and laboratory findings.

Table 1. Clinical examination findings of the patient

Parameters	Findings	Interpretation
Pallor	Present	Anemia
Icterus	Equivocal	+/- Jaundice
Cyanosis	Absent	Normal
Pedal edema	Absent	Normal
Clubbing	Absent	Normal
Lymphadenopathy	Not present	Normal
Blood pressure	156/90 mm Hg	hypertension
Pulse	90	Normal
Respiratory rate	22/minute	Normal

Table 2. Hematological findings and iron profile of the patient

Parameters	Result (at the time of hospitalization)	Normal Reference Range/Pattern	Interpretation
Hemoglobin	9.8 g/dL	14-16 g/dL	Anemia
RBC count	5.1 million cells /mm^3	4-6 million cells/mm^3	Normal
HCT	30.7%	37-54%	Decreased
MCV	60.3 fl	80-100 fl	Decreased
MCH	19.3 pg	27-34 pg	Decreased
MCHC	32 g/dL	32-36	Decreased
Mentzer index (MCV/RBC count)	11.8	< 13 seen in thalassemia > 13 seen in iron deficiency anemia	Suggesting β thalassemia
WBC	8870 cells/mm^3	4000-11000 cells/mm^3	Normal
Lymphocyte	7.1%	20-40 %	Decreased
Neutrophils	90.2%	50-70%	Increased
Platelet count	1.59 lac cells/cu mm	1-4 lacs/mm^3	Normal
Peripheral smear picture	Microcytic hypochromic RBCs	Normocytic normochromic RBCs	Microcytic hypochromic anemia
Serum iron	97.7 µg/dL	65-175 µg/dL	Normal
Serum ferritin	320.5 ng/mL	24-336 µg/L	Normal

Table 3. Hemoglobin fractions using high-performance liquid chromatography (HPLC)

Hemoglobin Fractions	Area %	Normal Reference Range	Peak Area Value	Interpretation
HbA1c	Not detected	4-5.6%	Not detected	Indicative of a genetic hemoglobinopathy
HbA0	7.0%	95-98%	118059	Drastically decreased
HbA2	5.5%	2-3%	84191	Increased
HbF	2.7%	< 0.5%	44054	Increased
HbD (retention time: 3.89 min)	74%	Normally not present	1229758	Increased
Unknown peak (retention time: 17.79 min)	5.9 %	-	97452	-

Table 4. Cardiac profile of the patient

Tests	Results	Normal Reference Range/Finding	Interpretation
NT ProBNP	949 pg/mL	65-175 pg/mL	Suggestive of congestive heart failure
Troponin I	< 0.1 ng/mL	< 0.1 ng/mL	Myocardial infarction was ruled out.
ECG	P-wave inversion	Non-inverted P wave	Cardiac disorder
Echocardiography	Severe left ventricular systolic dysfunction, ejection fraction 20-25%, trivial mitral regurgitation, dilated left atrium and left ventricle	Ejection fraction ≥ 60 %	Dilated cardiomyopathy
Chest X-ray	The heart showed enlargement, and the lungs showed congestion.	Clear lung fields	Cardiac disorder

Table 5. Other biochemical test results of the patient

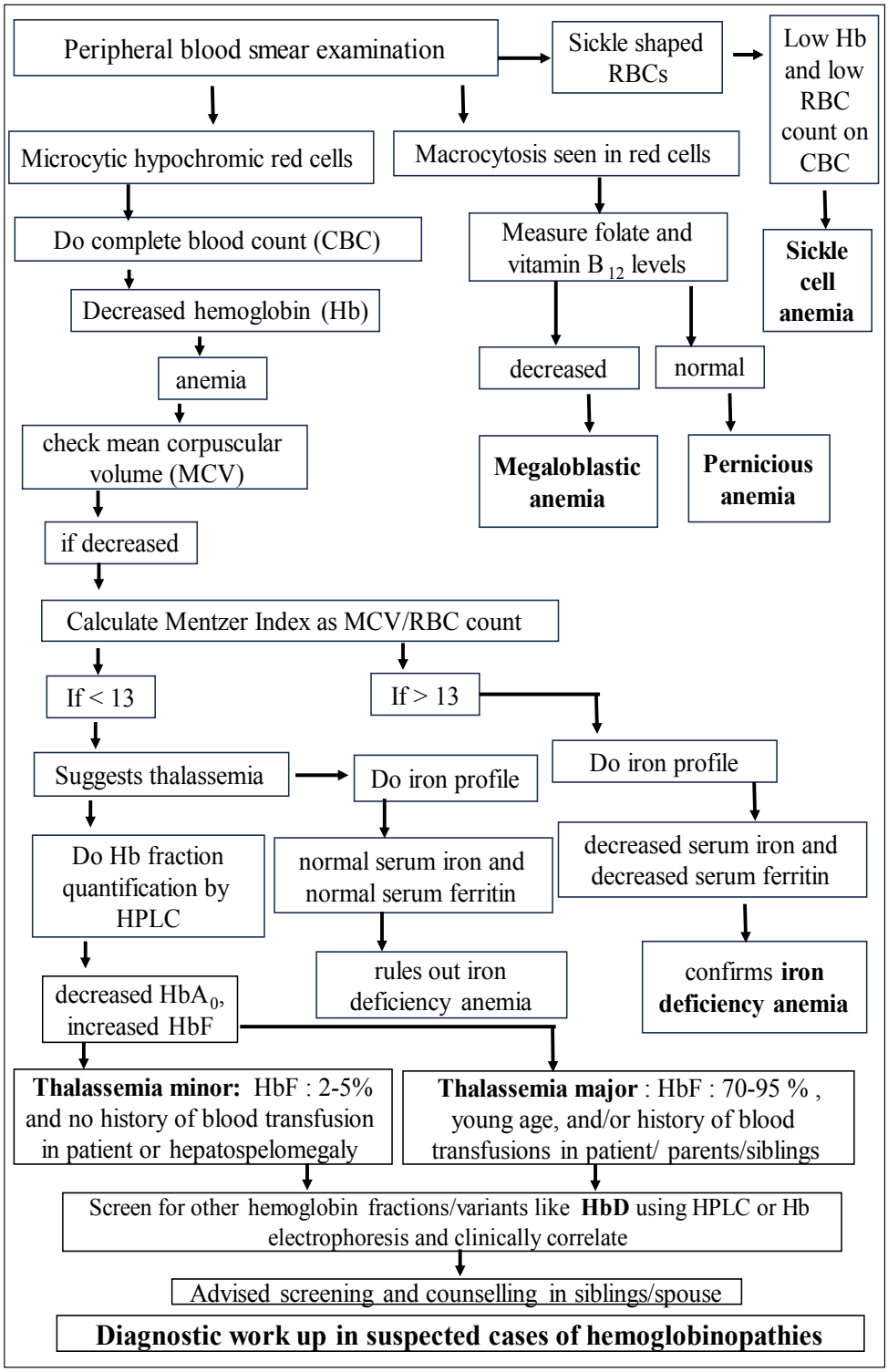
Tests	Results	Normal Reference Range/Reaction	Interpretation
Glycemic profile RBS	216 mg/dL	< 140 mg/dL	Diabetic range
Renal function tests Urea Creatinine	57.7 mg/dL 1.1 mg/dL	15-45 mg/dL 08-1.1 mg/dL	Slightly high normal
Serum electrolytes Na^+ K^+ Cl^-	 133 mmol/L 4.3 mmol/L 102 mmol/L	 136-145 mmol/L 3.5-5.1 mmol/L 98-107 mmol/L	 Normal Normal Normal
Liver function test Total bilirubin Direct bilirubin Indirect bilirubin ALT AST ALP Total protein Albumin Globulin	 1.7 mg/dL 0.7 mg/dL 1 mg/dL 30 IU/L 24 IU/L 43 IU/L 7.0 mg/dL 4.2 mg/dL 2.8 mg/dL	 0.3-1 mg/dL 0.1-0.3 mg/dL 0.2-0.8 mg/dL < 45 U/L < 35 U/L 53-128 U/L 6.4-8.3 mg/dL 3.5-5.2 mg/dL 2.5-3.5 mg/dL	 Normal Normal Slightly increased Normal Normal Normal Normal Normal Normal
HbsAg	Negative	Negative	Normal
HIV	Negative	Negative	Normal
HCV	Negative	Negative	Normal

The reference values for random blood sugar (RBS), renal function tests, liver function tests (LFTs), and electrolytes were obtained from *Teitz Textbook of Clinical Chemistry and Molecular Diagnostics* and *Mosby's Diagnostic & Laboratory Test Reference* (15th edition) on VitalSource.

Table 6. Urine examination findings of the patient

Urine Physical and Chemical Findings and Stool Examination Findings			**Urine Microscopic Examination**		
Parameters	***Results***	***Interpretation***	***Parameters***	***Results***	***Interpretation***
Turbidity	Nil	Normal	RBCs	nil	Normal
Color	Oale yellow	Normal	Pus cells	2-5 cells/hpf	Normal
Deposits	Nil	Normal	Epithelial cells	2-5 cells/hpf	Normal
Sugar	Negative	Normal	Casts	Nil	Normal
Protein	Negative	Normal	Crystals	Nil	Normal
Ketone bodies	Negative	Normal	Amorphous deposits	Nil	Normal
Stool for occult blood	Positive	Abnormal			

Figure 1. The algorithm shows the diagnostic workup in a suspected case of hemoglobinopathy.



Discussion

The patient exhibited clinical signs of anemia, which aligned with the hematological findings (Table 2). The hemoglobin level was 9.8 g/dL, and peripheral blood smear examination revealed microcytic, hypochromic red blood cells (RBCs). A stool examination further indicated occult blood loss. The patient's mean corpuscular volume (MCV) was also reduced. The Mentzer index, calculated as the ratio of MCV to RBC count, was <13, suggesting thalassemia.[5] Further analysis of the iron profile revealed that serum iron and serum ferritin levels were within the normal reference range. Since the Mentzer index was not greater than 13, the possibility of iron deficiency anemia was ruled out.

The data presented in Table 3 demonstrate that the fraction of HbA0 (adult hemoglobin consisting of $\alpha 2\beta 2$) was significantly low (7.0%), which explains why HbA1c could not be detected. Furthermore, other hemoglobin fractions, including HbA2 (5.5%), HbF (2.7%), and HbD (74%), were elevated. An assessment of cardiac biomarkers revealed an increase in NT-ProBNP levels, indicative of congestive heart failure.

Echocardiography revealed dilated cardiomyopathy with left ventricular systolic dysfunction, mitral regurgitation, congestive heart failure, and a reduced ejection fraction of 20% to 25% (Table 4). ECG changes and chest X-ray findings (lung congestion) were consistent with the cardiac presentation. Table 5 indicates that the patient was diabetic, with a random blood sugar level of 216 mg/dL. Other tests, including renal function tests, serum electrolytes, and urine examination, were within normal limits (Table 5), except for a slight increase in serum urea, likely due to pre-renal causes such as dehydration resulting from dyspnea. Liver function tests were normal, except for mildly elevated total bilirubin (1.7 mg/dL) and indirect bilirubin levels, which may be attributed to a predisposition to mild hemolytic anemia associated with HbD.[4] The patient also tested negative for infective liver pathologies, such as hepatitis B and C (Table 5).

The diagnostic findings in this case pointed toward compound heterozygous HbD with a thalassemia trait. Although genetic studies could not be conducted to confirm this definitively, the HbD levels being below 92% suggested a heterozygous HbD variant.[6] Moreover, the absence of a clinical history of blood transfusions in the patient or his family members, coupled with HbF levels that were not significantly elevated (as typically seen in thalassemia major, where levels can reach up to 95%), further supported the likelihood of a thalassemia trait.[7] These findings collectively indicate a probable diagnosis of compound heterozygous HbD with thalassemia trait.

A review of the literature indicates that most cases of isolated HbD or thalassemia trait remain asymptomatic throughout life. However, when co-inherited with another hemoglobin variant, such as sickle cell or thalassemia, it can lead to clinically significant conditions that often require hospital admissions and blood transfusions.[4] In this case, the patient presented late with cardiac involvement, resulting in lung congestion and manifesting as sudden-onset dyspnea accompanied by a severely reduced ejection fraction (20%–25%). This can be attributed to the genetically depressed levels of normal adult hemoglobin (HbA0), which place an additional burden on the cardiovascular system to pump blood to the lungs for adequate oxygenation. Over time, this chronic strain can lead to dilated cardiomyopathy, congestive heart failure, and lung congestion due to hemodynamic changes.

Additionally, the patient exhibited occult blood in the stool, the cause of which was not investigated in this case. A study by Kalyan et al[8] similarly reported occult blood loss in stools due to hemorrhoids in a patient with coexisting HbD and thalassemia trait. An accurate diagnosis and reporting of hemoglobinopathies are often hindered by limitations such as the availability and affordability of genetic testing for hemoglobin alleles in laboratories. Therefore, a comprehensive approach involving detailed history-taking, thorough clinical examination, and diagnostic laboratory findings plays a crucial role. To assist healthcare professionals in the diagnostic workup of suspected hemoglobinopathies, we have developed an algorithm, as illustrated in the accompanying figure 1.

Regarding the cardiac presentation, differential diagnoses such as ischemic cardiomyopathy, diabetic cardiomyopathy, and myocarditis were considered. Ischemic cardiomyopathy is a cardiac condition caused by prolonged myocardial ischemia due to coronary artery disease, resulting in heart failure and reduced ejection fraction. The patient did not undergo angiography or coronary computed tomography angiography during this visit as he did not exhibit typical symptoms of ischemic heart disease, such as angina. Hence, we primarily relied on noninvasive clinical assessments for evaluation. Coronary angiography was planned for a subsequent visit; however, the patient was lost to follow-up.

Myocarditis, an inflammation of the myocardium typically caused by viral infections, can also result in severe left ventricular systolic dysfunction. Still, the patient did not exhibit clinical symptoms or a history suggestive of a recent viral infection or myocarditis. Furthermore, no elevated inflammatory markers were observed in this case. Thus, based on the clinical presentation, myocarditis was considered a less likely differential diagnosis.

Diabetic cardiomyopathy is a form of heart dysfunction associated with diabetes, characterized by myocardial stiffness, impaired relaxation, and eventual heart failure, independent of coronary artery disease. Although cardiac magnetic resonance imaging was planned for further assessment in this patient, he was lost to follow-up. As a result, we primarily relied on the clinical presentation, which was consistent with diabetes, to guide our evaluation.

Conclusion

This case, reported from the Bathinda region of Punjab, involves a patient with coexisting HbD and thalassemia trait (compound heterozygous) who presented later in life with dilated cardiomyopathy, congestive heart failure, dyspnea, and anemia. Based on clinical assessment, ischemic cardiomyopathy and myocarditis were deemed less likely due to the absence of typical symptoms and inflammatory markers. Further evaluation of potential differential diagnoses was limited, as the patient was lost to follow-up before advanced imaging could be conducted. The cardiac

dysfunction observed in this case may represent a late sequela of heart failure secondary to chronic anemia caused by underlying hemoglobinopathies. However, more evidence from similar case reports and studies is needed to substantiate this association and fully elucidate its clinical implications.

Conflict of Interest

The authors declare that there is no conflict of interest

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