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Case Report

Recurrent Iron Deficiency Anemia in a Patient with Hb D-Punjab Trait Receiving Tirzepatide

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Abstract

Background: Hemoglobin D-Punjab (Hb D-Punjab, also known as Hb D-Los Angeles) is an uncommon structural β -globin variant that is typically clinically silent in the heterozygous state and is not associated with iron deficiency. Recurrent iron deficiency anemia (IDA) despite appropriate oral and intravenous iron replacement warrants a comprehensive evaluation for chronic blood loss, malabsorption, nutritional deficiency, and coexisting hematologic disorders. With the increasing use of incretin-based therapies such as tirzepatide for obesity management, reduced dietary intake has emerged as a potential contributor to micronutrient deficiencies in susceptible individuals. **Case Presentation:** A 47-year-old woman presented with persistent microcytic hypochromic anemia and recurrent depletion of iron stores despite repeated courses of oral and intravenous iron therapy. Serial laboratory investigations demonstrated hemoglobin values ranging from 11.78 to 13.2 g/dL, with persistent microcytosis (MCV 72.7–77.1 fL), relatively elevated red blood cell counts ($4.82\text{--}5.42 \times 10^{12}/\text{L}$), and recurrently low ferritin levels (as low as 3.1 ng/mL). Hemoglobin electrophoresis demonstrated heterozygous Hb D-Punjab trait (Hb D 40.4%), while persistent microcytosis with a relatively elevated red blood cell count suggested possible coexisting α -thalassemia trait. Evaluation excluded celiac disease, thyroid dysfunction, vitamin B12 deficiency, and gynecological pathology. The patient denied gastrointestinal symptoms but had not undergone endoscopic gastrointestinal evaluation. She had been receiving tirzepatide for weight management, raising the possibility that prolonged appetite suppression and reduced dietary iron intake may have contributed to recurrent iron deficiency, although a causal relationship cannot be established. **Conclusion:** This case highlights the importance of confirming true biochemical iron deficiency rather than attributing anemia to an incidental hemoglobin variant. Recurrent IDA despite adequate iron replacement requires systematic evaluation for gastrointestinal blood loss, nutritional deficiency, malabsorption, gynecological disorders, and coexisting hematologic conditions. As incretin-based therapies become increasingly used for obesity management, clinicians should remain aware of the potential for nutritional deficiencies in susceptible patients and ensure appropriate clinical and nutritional follow-up.

Keywords: Hemoglobin D-Punjab; Iron deficiency anemia; Tirzepatide; Obesity; Hemoglobinopathy; Microcytic anemia; α -thalassemia trait.

INTRODUCTION

Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide and remains a leading cause of anemia in adults. Although most patients respond to oral or intravenous iron replacement, recurrent or persistent iron deficiency despite apparently adequate therapy warrants a comprehensive evaluation for ongoing blood loss, malabsorption, inadequate dietary intake, chronic inflammatory conditions, and less common hematologic disorders ^{1,2}. Establishing the underlying etiology is essential to prevent repeated iron depletion and unnecessary treatment. Hemoglobin D-Punjab (Hb D-Punjab), also known as Hb D-Los Angeles, is an uncommon structural β -globin variant caused by a missense mutation in the β -

globin gene that results in substitution of glutamine for glutamic acid at codon 121 ($\beta 121 \text{ Glu} \rightarrow \text{Gln}$) ³. In the heterozygous state, Hb D-Punjab is generally considered clinically benign and is not associated with iron deficiency or clinically significant anemia ⁴. However, the coexistence of Hb D-Punjab with other inherited red cell disorders, such as α -thalassemia, may produce persistent microcytosis and complicate the interpretation of hematologic indices ⁵.

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has become an effective pharmacologic therapy for obesity because of its substantial effects on weight reduction ^{6,7}. Its mechanism of action includes appetite suppression and delayed gastric emptying,

leading to reduced caloric intake. Although iron deficiency is not a recognized adverse effect of tirzepatide, prolonged reductions in dietary intake may theoretically contribute to micronutrient deficiencies in susceptible individuals, particularly when additional risk factors for iron depletion are present ⁸.

We report the case of a 47-year-old woman with recurrent biochemical iron deficiency despite repeated oral and intravenous iron replacement, in whom heterozygous Hb D-Punjab trait was identified during the diagnostic workup. The case highlights the importance of distinguishing incidental hemoglobin variants from the true cause of iron deficiency, considering coexisting hematologic disorders, and performing a systematic evaluation before attributing recurrent anemia to a single etiology. It also raises the possibility that reduced dietary intake during tirzepatide therapy may represent a contributing factor in selected patients, although a causal relationship cannot be established.

CASE PRESENTATION

A 47-year-old woman was referred to the hematology clinic for evaluation of recurrent iron deficiency anemia that had persisted for more than one year despite repeated courses of oral iron supplementation and intermittent intravenous iron replacement. Although hemoglobin and ferritin levels improved after treatment, both declined repeatedly during follow-up, indicating recurrent depletion of iron stores despite apparently adequate replacement therapy.

Her medical history was significant for obesity, for which she had been receiving tirzepatide 10 mg once weekly for the preceding eight months as part of a weight-management program. She had no history of diabetes mellitus, chronic kidney disease, inflammatory

bowel disease, gastrointestinal surgery, chronic liver disease, or autoimmune disorders. She was not taking proton pump inhibitors, nonsteroidal anti-inflammatory drugs, anticoagulants, or other medications known to interfere with iron absorption or increase the risk of gastrointestinal bleeding.

She reported regular menstrual cycles without heavy menstrual bleeding or intermenstrual bleeding. She denied melena, hematochezia, hematemesis, abdominal pain, dysphagia, chronic diarrhea, or other gastrointestinal symptoms. There was no history of unintentional weight loss before initiating tirzepatide therapy. Information regarding family history of hemoglobinopathies or inherited anemia was unavailable.

On physical examination, the patient was hemodynamically stable and appeared well. There was no clinically significant pallor, jaundice, lymphadenopathy, hepatosplenomegaly, or peripheral edema. The remainder of the systemic examination was unremarkable.

Serial laboratory investigations demonstrated persistent microcytic hypochromic indices with recurrent biochemical iron deficiency (Table 1). Hemoglobin values ranged from 11.78 to 13.2 g/dL over the observation period. Microcytosis was already present in August 2024 (MCV 77.1 fL) and persisted through subsequent evaluations (MCV 72.7–76.9 fL), accompanied by relatively elevated red blood cell counts (approximately $4.82\text{--}5.42 \times 10^{12}/\text{L}$) and elevated red cell distribution width. Serial ferritin measurements showed values as low as 3.1 ng/mL, with subsequent levels of 7.8 and 8.4 ng/mL, all below the laboratory reference range (11–306.8 ng/mL), confirming recurrent depletion of iron stores despite intermittent replacement therapy.

Table 1. Serial hematological and iron-related investigations

Date	Hb (g/dL)	RBC ($\times 10^{12}/\text{L}$)	MCV (fL)	MCH (pg)	RDW (%)	Ferritin (ng/mL)	Interpretation
06 Aug 2024	12.75	5.03 ↑	77.1 ↓	25.3 ↓	15.9 ↑	—	Microcytosis and hypochromia with relatively high RBC count
06 Apr 2025	12.68	5.42 ↑	72.7 ↓	23.4 ↓	17.5 ↑	3.1 ↓	Severe depletion of iron stores with marked microcytosis
13 May 2025	11.94 ↓	4.82 ↑	74.4 ↓	24.8 ↓	18.8 ↑	—	Microcytic hypochromic anemia with marked anisocytosis
21 Dec 2025	11.78 ↓	4.93 ↑	74.8 ↓	23.9 ↓	16.9 ↑	—	Persistent microcytic hypochromic anemia
30 Mar 2026	13.2	5.25 ↑	73.7 ↓	25.1 ↓	18.8 ↑	7.8 ↓	Hb normalized but iron stores remained depleted with persistent microcytosis
09 Jun 2026	13.03	5.06 ↑	76.9 ↓	25.8 ↓	15.4 ↑	8.4 ↓	Persistent iron depletion and microcytosis despite preserved Hb

Thyroid function tests, serum vitamin B12 levels, and serologic screening for celiac disease were within normal limits (Table 2). Pelvic ultrasonography demonstrated no structural gynecological abnormalities that could account for chronic blood loss.

Table 2. Hemoglobin analysis and investigations for secondary causes

Investigation	Result	Interpretation
HbA	56.7%	Reduced relative proportion
HbA ₂	2.9%	Normal
Hb D-Punjab	40.4%	Pattern consistent with heterozygous Hb D trait
Anti-tissue transglutaminase IgA	<2 RU/mL	Negative
Deamidated gliadin IgA	<2 RU/mL	Negative
TSH	1.047 μ IU/mL	Normal
Vitamin B12	Normal	No evidence of B12 deficiency
Vitamin D	Previously low; corrected	Corrected following treatment
Pelvic ultrasonography	Normal	No structural gynecological abnormality identified
GI symptoms/overt bleeding	Absent	No melena or reported GI bleeding
PPI use	None	—

Hemoglobin electrophoresis demonstrated HbA 56.7%, HbA₂ 2.9%, and Hb D-Punjab 40.4%, confirming heterozygous Hb D-Punjab trait. Persistent microcytosis despite intermittent iron replacement, together with a relatively elevated red blood cell count, raised suspicion for coexisting α -thalassemia trait; however, molecular genetic testing was not performed to confirm the diagnosis.

Despite correction of iron deficiency following intravenous iron administration, iron stores became depleted again during follow-up. No overt source of chronic blood loss or malabsorption was identified during the initial evaluation. Although the patient denied gastrointestinal symptoms, upper and lower gastrointestinal endoscopic investigations had not been performed at the time of this report; therefore, occult gastrointestinal pathology could not be definitively excluded.

Given the absence of an identifiable cause of recurrent iron deficiency and the temporal association with prolonged tirzepatide therapy, reduced dietary iron intake secondary to sustained appetite suppression was considered a possible contributing factor. However, a causal relationship could not be established, and the recurrent iron deficiency was considered multifactorial pending further evaluation.

DISCUSSION

Hemoglobin D-Punjab (Hb D-Punjab), also known as Hb D-Los Angeles, is one of the most common structural hemoglobin variants after Hb S and Hb C, although its prevalence varies geographically and remains relatively low worldwide²². Heterozygous Hb D-Punjab is generally considered a clinically benign condition and is not associated with clinically significant anemia or iron deficiency^{4,22}. Consequently, the identification of Hb D-Punjab trait in a patient with recurrent iron deficiency anemia should not lead clinicians to attribute the anemia solely to the hemoglobin variant without objective evidence supporting such a relationship.

The principal diagnostic challenge in this case was distinguishing an incidental hemoglobinopathy from the underlying cause of recurrent biochemical iron deficiency. Although hemoglobin electrophoresis confirmed heterozygous Hb D-Punjab trait, persistent microcytosis despite repeated iron replacement, together with a relatively elevated red blood cell count, suggested the possibility of coexisting α -thalassemia trait. The longitudinal data reinforce this observation: microcytosis was already present in August 2024 (MCV 77.1 fL) and persisted across multiple time points through June 2026 (MCV 72.7–76.9 fL), while the RBC count remained relatively high (approximately $4.82\text{--}5.42 \times 10^{12}/\text{L}$). This mixed phenotype—unequivocal iron deficiency (ferritin as low as 3.1 ng/mL) plus persistent disproportionate microcytosis and elevated RBC count—warrants consideration of an additional inherited microcytic trait. Coinheritance of α -thalassemia with structural hemoglobin variants has been reported and may contribute to persistent microcytosis despite correction of iron deficiency^{5,21,24}. However, molecular genetic testing was not available in this case; therefore, the presence of α -thalassemia remains presumptive.

Recurrent iron deficiency despite apparently adequate oral and intravenous iron replacement should always prompt a systematic search for its underlying cause rather than repeated empirical iron therapy alone. The differential diagnosis includes chronic gastrointestinal blood loss, gynecological disorders, malabsorption syndromes such as celiac disease, nutritional deficiency, chronic inflammatory conditions, and less common hematologic disorders^{1,2,25,31}. In the present case, celiac disease, thyroid dysfunction, vitamin B12 deficiency, and structural gynecological abnormalities were excluded. The patient also denied symptoms suggestive of gastrointestinal bleeding or malabsorption. However, because upper and lower gastrointestinal endoscopic evaluations had not been performed, occult gastrointestinal pathology cannot be definitively

excluded and remains an important limitation of this report.

The patient's use of tirzepatide introduced an additional diagnostic consideration. Tirzepatide, a dual glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, promotes weight loss primarily through appetite suppression and delayed gastric emptying^{6,7}. Although iron deficiency is not a recognized adverse effect of tirzepatide, sustained reductions in food intake may theoretically reduce dietary iron consumption in susceptible individuals, particularly premenopausal women or those with marginal baseline iron stores. At present, there is insufficient evidence to establish a causal relationship between tirzepatide therapy and recurrent iron deficiency anemia. Therefore, in this case, tirzepatide should be regarded only as a potential contributing factor rather than the primary cause of the patient's recurrent iron deficiency.

This case underscores the importance of interpreting hematologic investigations in their clinical context. Incidental identification of a hemoglobin variant should not divert attention from the systematic evaluation required for recurrent iron deficiency. Confirmation of biochemical iron deficiency with ferritin and iron studies, careful interpretation of red cell indices, and exclusion of common causes of recurrent iron loss remain essential before attributing anemia to inherited hemoglobin disorders or medication use.

To our knowledge, reports describing recurrent iron deficiency anemia in patients with heterozygous Hb D-Punjab receiving tirzepatide are extremely limited. Although this case does not establish a causal association between tirzepatide and iron deficiency, it highlights a clinically relevant diagnostic scenario in which an incidental hemoglobinopathy, possible coexisting α -thalassemia trait, and reduced nutritional intake may coexist. Further observational studies are needed to determine whether prolonged treatment with incretin-based therapies influences iron homeostasis in susceptible individuals.

CONCLUSION

This case highlights the importance of not attributing recurrent iron deficiency anemia to an incidental hemoglobin variant without thorough evaluation and confirmation of true biochemical iron deficiency. In patients with persistent or recurrent iron deficiency despite adequate iron replacement, a systematic diagnostic approach is essential to exclude ongoing blood loss, malabsorption, nutritional deficiency, gynecological disorders, and coexisting hematologic conditions.

The coexistence of heterozygous Hb D-Punjab trait and possible α -thalassemia trait in this patient contributed to persistent microcytosis and added complexity to the interpretation of hematologic indices. Serial laboratory data documenting microcytosis from August 2024 through June 2026, together with recurrently low ferritin levels (3.1–8.4 ng/mL), strengthen the observation of a mixed phenotype of iron deficiency

plus an inherited microcytic trait. Although the patient was receiving tirzepatide for weight management, its role in recurrent iron deficiency remains speculative, and a causal relationship cannot be established based on a single case.

Clinicians should be aware that pharmacologically induced weight loss and appetite suppression may contribute to reduced micronutrient intake in susceptible individuals. However, further studies are required to clarify any potential association between incretin-based therapies and iron metabolism. A comprehensive, multidisciplinary approach remains essential in the evaluation of unexplained or recurrent iron deficiency anemia.

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