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# Early Neonatal Presentation and Management of Diamond-Blackfan Anemia: A Case Report

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## Abstract

Diamond-Blackfan anemia (DBA) is a rare congenital red cell aplasia that may present with severe anemia in early infancy. This report describes a case with very early neonatal presentation and a favorable hematologic response to corticosteroid therapy. A term male infant was presented at two days of life with marked pallor, feeding refusal, and severe anemia, with a hemoglobin level of 6.7 g/dL, requiring a red blood cell transfusion. After recurrent episodes of severe anemia, further investigation demonstrated macrocytosis, reticulocytopenia, and a normocellular bone marrow with rare erythroblasts, supporting the diagnosis of DBA. Oral prednisolone was initiated at one month 15 days of age and was associated with subsequent hematologic improvement, allowing gradual dose reduction. At the latest follow-up, the patient was 17 months old and had remained transfusion-independent for 14 months while receiving maintenance prednisolone.

This case highlights the importance of considering DBA in neonates with unexplained severe anemia and reticulocytopenia, even in the absence of congenital anomalies. The hematologic response and sustained transfusion independence demonstrate a favorable clinical course following individualized management, with continued follow-up needed to assess long-term response and treatment safety.

**Categories:** Hematology, Pediatrics
**Keywords:** diamond-blackfan anemia, neonatal anemia, pediatric hematology, pure red cell aplasia (prca), reticulocytopenia

## Introduction

Diamond-Blackfan anemia (DBA) is a rare congenital pure red cell aplasia, with an estimated incidence of five to 10 cases per million live births, characterized by macrocytic anemia, reticulocytopenia, and selective erythropoietic failure [1,2]. It is classified as a ribosomopathy caused by pathogenic variants in ribosomal protein genes and may be accompanied by congenital anomalies, endocrine dysfunction, growth impairment, and cancer predisposition. Despite advances in understanding its molecular basis, DBA presents a central paradox: ribosomal proteins are ubiquitously expressed, yet their haploinsufficiency causes a predominantly erythroid defect through mechanisms that remain incompletely understood [3].

Establishing a diagnosis of DBA in the first weeks of life is particularly challenging because normal neonatal hematologic physiology substantially overlaps with the expected findings of the disease. Hemoglobin follows its own physiologic trajectory, reaching an expected nadir between six and 12 weeks of life, a period that overlaps with the reported median age at DBA diagnosis of approximately two to three months. Similarly, the physiologically high mean corpuscular volume (MCV) in neonates may obscure the recognition of disease-related macrocytosis. Age-related changes also limit the interpretation of supportive markers such as fetal hemoglobin (HbF), whose elevation is considered reliably assessable only in patients older than six months [2]. These age-dependent changes complicate the interpretation of anemia and macrocytosis in the neonatal period, underscoring the importance of assessing these findings alongside reticulocyte counts and bone marrow morphology [4]. Clinical presentation is also heterogeneous, with approximately 76% of patients manifesting anemia in infancy. Moreover, approximately 50% of cases lack typical congenital anomalies, such as microcephaly, hypertelorism, absent or atypical thumbs, polydactyly or syndactyly, cardiac malformations (most commonly septal defects), and genitourinary/renal malformations (including renal aplasia, horseshoe kidney, duplicated collecting system, and hypospadias), that could otherwise raise phenotypic suspicion [2].

Early recognition of this condition is clinically important because severe neonatal anemia often requires immediate transfusion support and a focused diagnostic workup to differentiate DBA from hemolytic disease, transient or infection-related erythroblastopenia, and other inherited or acquired causes of erythroid failure. Current management strategies include transfusional support, corticosteroid therapy, and hematopoietic stem cell transplantation in selected patients; treatment decisions must be individualized according to age, hematologic response, and risk of long-term complications. For this reason, reports of uncommon presentations and favorable treatment outcomes may provide useful clinical insights [5]. The present report aims to describe a case of early neonatal presentation of DBA and to discuss its diagnostic

and therapeutic challenges.

## Case Presentation

A term male infant was born by cesarean section (breech presentation) at 39 weeks of gestation following an uncomplicated pregnancy. Maternal blood type was O positive; the indirect antiglobulin test was negative, and serologic testing for HIV, syphilis, hepatitis B and C, cytomegalovirus, and toxoplasmosis was negative. Birth weight was 2.99 kg; Apgar scores were 8 and 9 at one and five minutes. At two days of life, after discharge, the infant presented with feeding refusal and marked pallor without jaundice. Initial laboratory evaluation at three days revealed hemoglobin of 6.7 g/dL, MCV of 136.9 fL, mean corpuscular hemoglobin (MCH) of 45.0 pg, and mean corpuscular hemoglobin concentration (MCHC) of 32.8 g/dL. He received a standard packed red blood cell (PRBC) transfusion (15 mL/kg) at three days and was hospitalized; the reticulocyte count at four days was 17.9 × $10^9$/L. During admission, he developed a urinary tract infection caused by coagulase-negative Staphylococcus, treated with a 10-day course of vancomycin. A second standard PRBC transfusion was given at 10 days for a hemoglobin level of 7.7 g/dL in the context of active infection; discharge occurred at 17 days. During outpatient follow-up, hemoglobin fell to 3.5 g/dL at one month and five days, leading to a third standard PRBC transfusion and referral to a tertiary hospital three days later.

Admission to the referral center occurred at one month and eight days for etiologic investigation. At this time, the hemoglobin level was 5.3 g/dL, the reticulocyte count was 19.2 × $10^9$/L, and the MCV was 95.3 fL. Physical examination revealed no congenital anomalies (Figure *1*), and abdominal and genitourinary ultrasonography, along with transthoracic echocardiography, showed no structural malformations. Hemolytic anemia was excluded by a negative direct antiglobulin (Coombs) test and age-appropriate bilirubin levels, with concurrent reticulocytopenia supporting a regenerative anemia. Viral-associated red cell aplasia, nutritional deficiency, and hemoglobinopathy were excluded by negative serologies (parvovirus B19, HIV-1/2, hepatitis B and C, cytomegalovirus, herpes simplex virus, and toxoplasmosis), normal iron studies, normal folate and vitamin B12 levels, and normal hemoglobin electrophoresis in the patient and both parents. Family history was unremarkable for anemia or other hematologic disorders. Transient erythroblastopenia of childhood was considered unlikely given the patient's age and persistent course (differential diagnosis and exclusion workup summarized in Table *1*). Bone marrow examination demonstrated normocellularity with rare erythroblasts and preserved granulocytic and megakaryocytic lineages, supporting pure red cell aplasia consistent with DBA, without evidence of generalized marrow involvement. During inpatient evaluation, the infant developed recurrent hemoglobin levels below 7.0 g/dL (5.3 and 6.6 g/dL) and received two leukoreduced irradiated PRBC transfusions at one month and eight days and one month and 11 days. Given the recurrent transfusion requirement, prednisolone was initiated at 1 mg/kg/day at one month and 15 days. Hemoglobin subsequently reached 7.9 g/dL, allowing hospital discharge at one month and 17 days.

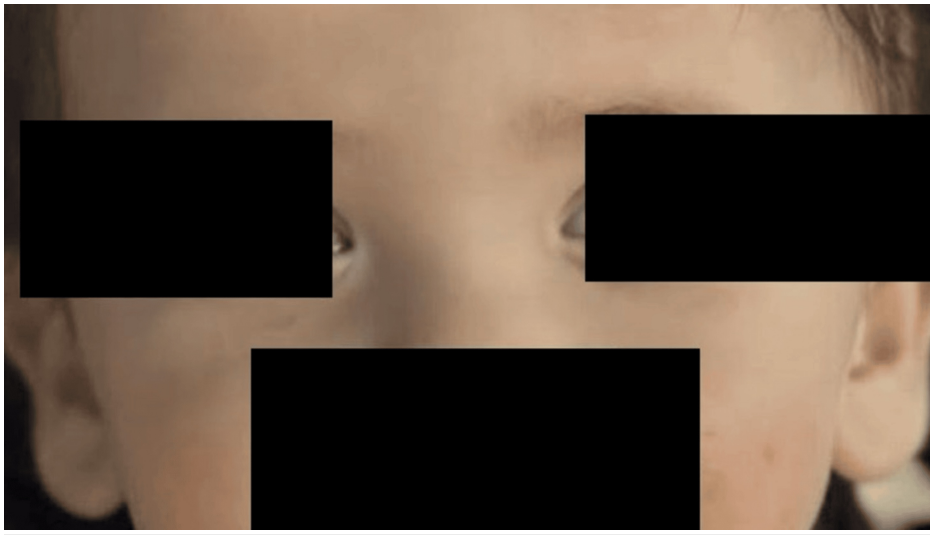


**FIGURE 1: Craniofacial appearance of the patient**

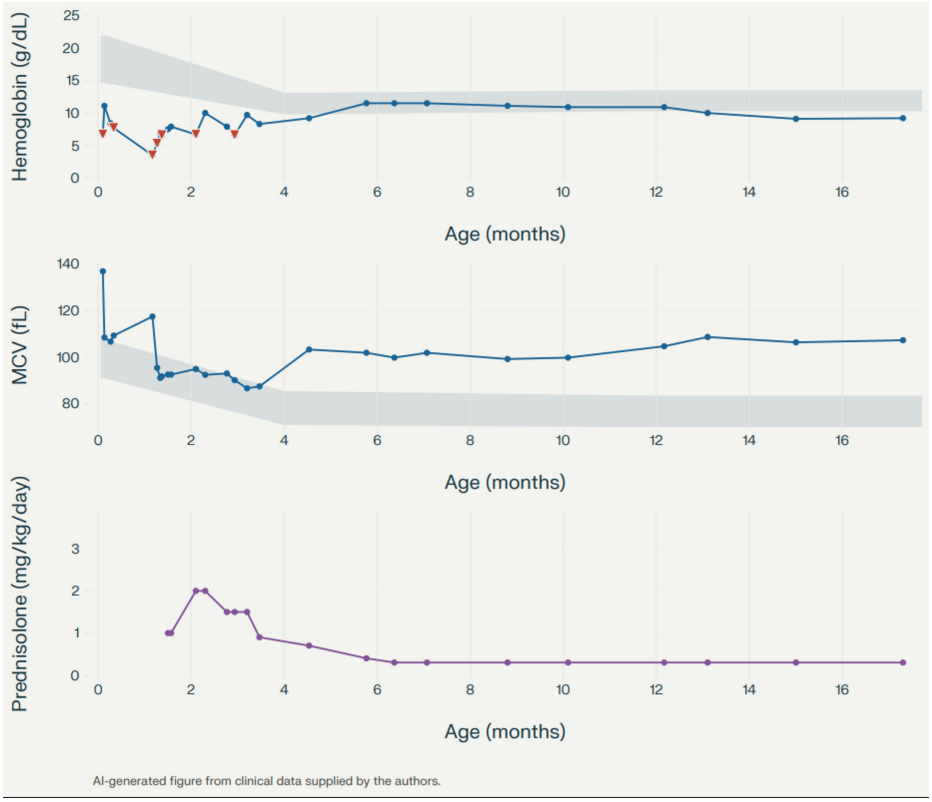
Absence of facial dysmorphism, with normal epicanthal folds and auricular implantation. Facial features were obscured for confidentiality. Written informed consent for publication was obtained from the patient's legal guardians.

| Differential Diagnosis | Excluded Based On |
|---|---|
| Hemolytic Anemia | Negative direct antiglobulin test; age-appropriate bilirubin levels and low reticulocyte count |
| Congenital or Perinatal Viral Infection | Negative serologic testing for TORCH pathogens, parvovirus B19, HIV-1/2, and hepatitis C virus |
| Transient Erythroblastopenia of Childhood (TEC) | Age <1 year at onset (atypical for TEC); persistent course without spontaneous recovery; erythroid hypoplasia on bone marrow examination |
| Inherited Bone Marrow Failure Syndromes (beyond DBA) | Isolated erythroid hypoplasia with preserved myeloid and megakaryocytic lineages on bone marrow examination |
| Hemoglobinopathy | Normal hemoglobin electrophoresis (patient and parents); negative family history for anemia |
| Nutritional Deficiency | Normal iron studies, vitamin B12, and folate levels |

**TABLE 1: Differential diagnosis and diagnostic workup for exclusion**

DBA: Diamond-Blackfan Anemia; TORCH: toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex

During early outpatient follow-up, hemoglobin remained around 7 g/dL (temporal trends shown in Figures *2*, *3*). An additional leukoreduced irradiated PRBC transfusion was required due to a hemoglobin level of 6.7 g/dL at two months and three days, prompting a prednisolone dose increase to 2 mg/kg/day. Following this adjustment, the patient exhibited progressive hematologic improvement, allowing gradual tapering. During tapering, however, hemoglobin declined to 6.6 g/dL at two months and 28 days, requiring a seventh and final PRBC transfusion using a leukoreduced irradiated component. Thereafter, tapering continued successfully to a maintenance dose of 0.3 mg/kg/day. Hemoglobin remained stable at approximately 9-11 g/dL over the last 13 months, with no transfusions required in the last 14 months. Throughout follow-up, the patient was monitored for potential corticosteroid-related adverse effects, including growth parameters (weight, height, and growth velocity), metabolic profile (glucose, lipid panel, and electrolytes), bone health (clinical signs of fragility), signs of immunosuppression (recurrent or opportunistic infections), and clinical features suggestive of hypothalamic-pituitary-adrenal axis suppression. No adverse events were identified other than oral candidiasis at three months, which resolved with nystatin oral suspension, and language delay, which is currently under investigation. Weight and height have remained within Z-scores of 0 and +1 for age, indicating adequate proportional growth. The patient, now 17 months of age, remains under regular follow-up at a referral hematology center.




## FIGURE 2: Serial hemoglobin, MCV, and prednisolone doses during follow-up

MCV: mean corpuscular volume; red triangles: measurements followed by blood transfusion; gray shading represents reference intervals reported by Larsson et al. [4] at 48–118 hours, four months, and 12 months; reference limits were linearly interpolated between these ages for visualization.

The figure was created using Perplexity (Perplexity AI, Inc., CA, USA) based on the clinical data provided by the author. The figure was subsequently reviewed and validated before submission.

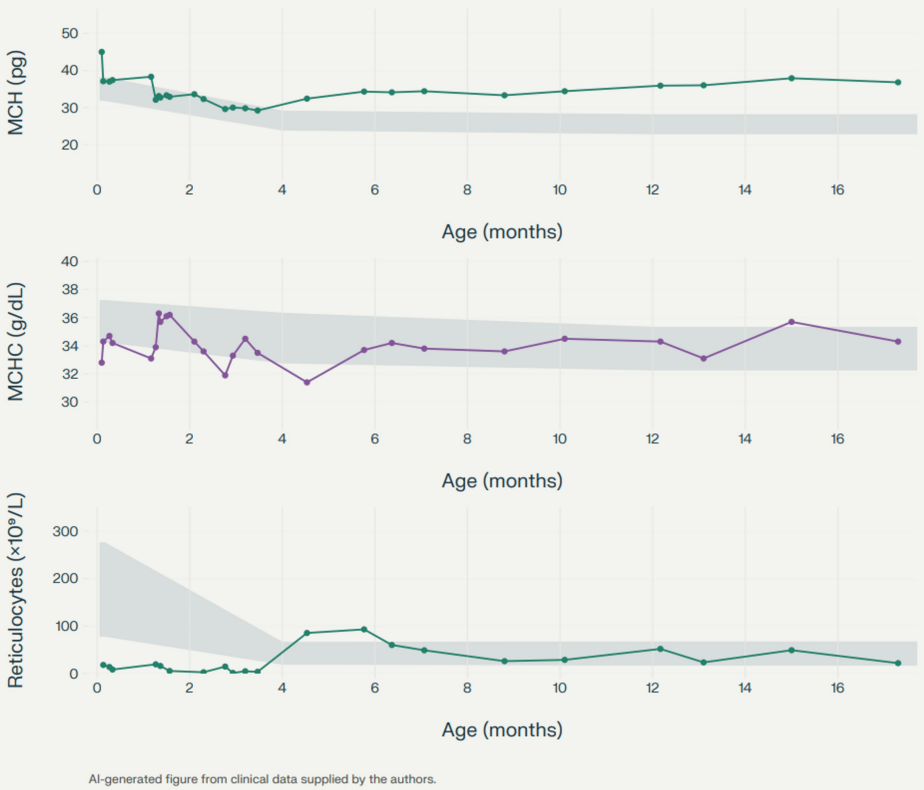



**FIGURE 3: Serial MCH, MCHC, and reticulocyte counts during follow-up**

MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; gray shading represents reference intervals reported by Larsson et al. [4] at 48–118 hours, four months, and 12 months; reference limits were linearly interpolated between these ages for visualization.

The figure was created using Perplexity (Perplexity AI, Inc., CA, USA) based on the clinical data provided by the author. The figure was subsequently reviewed and validated before submission.

## Discussion

DBA is characterized by macrocytic anemia, reticulocytopenia, and bone marrow erythroblastopenia with preserved cellularity [1]. In the present case, presentation at two days of life, together with the characteristic hematologic and bone marrow findings, supported the diagnosis of DBA. This timing is particularly noteworthy, as DBA is typically recognized within the first months of life, with a median age at diagnosis of two to three months [2,6]. Although only 10% of DBA cases are anemic at birth [7], this patient's presentation at two days of life falls within this rare neonatal-onset spectrum, well before the 56 days reported by Zhou et al. and the one to two months described by Da Costa et al. [8,9]. This earlier onset carries clinical relevance, as prompt diagnosis may allow earlier therapeutic intervention, reducing the risk of complications from severe anemia and recurrent transfusions [7].

According to the 2024 international consensus, the diagnosis of DBA can be established either by the identification of a pathogenic variant in a DBA-associated gene or by the presence of characteristic hematologic findings (macrocytic anemia with reticulocytopenia and bone marrow erythroblastopenia) after exclusion of other differential diagnoses [2]. In the present case, all characteristic features were present, and although a genetic panel was not available in this setting, clinical and laboratory evaluation did not support alternative diagnoses such as transient erythroblastopenia of childhood, infectious red cell aplasia, hemolysis, hemoglobinopathy, nutritional deficiency, or generalized bone marrow failure (Table *1*). Despite the absence of genetic confirmation, the clinical and laboratory findings support DBA as the most consistent diagnostic interpretation [2,10].

Macrocytosis, a characteristic feature of DBA, was evident from the first laboratory evaluation, at three days (136.9 fL), and declined toward the upper limit of normal on subsequent laboratory testing, possibly reflecting the effects of transfusions. Recent transfusions limit attribution of the initial hemoglobin increases to prednisolone alone, making the subsequent transfusion-free course more informative for assessing the hematologic response. Macrocytosis was consistently observed again from four months and 16 days of age onward (following 48 days without transfusion) when MCV ranged from 99.1 to 108.6 fL, exceeding the age-specific reference intervals (91-107 fL at 48-118 hours, 71-85 fL at four months, and 70-83

fL at 12 months) [4,11]. Concurrently, reticulocytopenia persisted through three months and 14 days of age, with the first documented normalization at four months and 16 days and intermittently low counts thereafter (absolute reticulocyte reference values: 74-442 × $10^9$/L at zero to seven days of age; 32-115 × $10^9$/L from seven days to 18 years) [12].

Management of DBA is primarily based on red blood cell transfusions in early infancy, corticosteroid therapy in older infants and children, and hematopoietic stem cell transplantation in selected cases [2]. In the case described by Zhou et al., corticosteroid therapy was deferred during infancy, and the patient remained transfusion-dependent [9]. In broader reports, including the review by Da Costa et al., therapeutic trajectories have been heterogeneous, ranging from transient steroid responsiveness to prolonged response with later treatment independence, persistent steroid requirement, and chronic transfusion dependence [8]. In contrast, this patient reached the therapeutic target range (>9-10 g/dL) [2] by four months of age and remained stable thereafter, even after tapering prednisolone to 0.3 mg/kg/day, a dose within the recommended maintenance range, which supported a favorable hematologic response to early steroid therapy [5]. However, this apparent benefit must be interpreted cautiously, as follow-up after the achievement of transfusion independence was limited to 14 months, which may still fall within an initial response period and may not predict durable long-term steroid responsiveness. This caution is warranted given that, although 60-80% of patients show initial steroid responsiveness, only 20-30% maintain a durable long-term response [13]. Corticosteroid initiation at one month and 15 days departed from current recommendations. An early therapeutic trial was initiated because severe anemia had recurred despite repeated transfusion support, with five transfusions required before treatment initiation, including three between one month and five days and one month and 11 days. The aim was to reduce the anticipated burden of continued transfusions and cumulative donor exposure. This potential benefit must be weighed against the risks of early corticosteroid exposure, including growth impairment, adrenal suppression, adverse effects on bone health, and increased susceptibility to infection. Continued transfusion support remained an alternative; this individualized decision should not be interpreted as evidence that early corticosteroid therapy was safer or preferable. Oral candidiasis occurred during treatment and resolved with nystatin. Language delay was also observed and remains under investigation; a causal relationship with corticosteroid exposure has not been established [2,14-16].

An additional point that warrants emphasis is that the favorable steroid response in the present case was biologically unexpected. Data from the Canadian Inherited Marrow Failure Registry identified age at diagnosis as the strongest predictor of steroid responsiveness, with responders diagnosed at a median age of 20 months versus three months among non-responders (optimal cutoff: 9.5 months) [17]. This patient, who manifested severe anemia at two days of life and started corticosteroid therapy at one month 15 days, falls well below this threshold. This apparent paradox suggests that factors other than age, such as genotype, may weigh more heavily in determining steroid response. RPL5 mutations are more common among non-responders and are associated with more congenital anomalies, whereas RPS19 (the most common genetic cause of DBA) is associated with better long-term steroid response [18]. The combination of absent congenital anomalies and favorable steroid responsiveness in this patient may indirectly suggest a lower likelihood of an RPL5 mutation, though this inference remains speculative without genetic confirmation.

A relevant limitation is the absence of genetic confirmation, as financial constraints affecting both the institution and the patient's family precluded molecular testing. The clinical diagnosis of DBA was supported by severe neonatal-onset macrocytic anemia, reticulocytopenia, and marked erythroid hypoplasia with preserved granulocytic and megakaryocytic lineages. Nevertheless, other congenital disorders of erythropoiesis could not be definitively excluded, and genotype-phenotype correlation was not possible. Molecular testing is expected to become available within the next year, which may permit retrospective genotype-phenotype correlation. An additional limitation is the relatively short follow-up period of 17 months, which may be insufficient to confirm durable steroid responsiveness or fully characterize the disease course.

## Conclusions

DBA should be considered in neonates with unexplained severe anemia and reticulocytopenia, even in the absence of congenital anomalies or a suggestive family history. Presentation at two days of life illustrates the diagnostic challenges associated with recognizing the disease in the immediate neonatal period. The recurrent transfusion requirement, characteristic hematologic findings, and selective bone marrow erythroblastopenia supported the clinical diagnosis despite the unavailability of molecular testing.

Corticosteroid therapy was associated with hematologic improvement and 14 months of transfusion independence, with gradual tapering to maintenance prednisolone. This course documents sustained hematologic improvement during treatment, but corticosteroid responsiveness is not specific to DBA and does not establish the diagnosis or exclude alternative causes of erythroid aplasia. However, corticosteroid initiation in early infancy departed from current recommendations, and the outcome observed here should be interpreted as an individual clinical experience rather than evidence supporting routine neonatal corticosteroid use. Long-term follow-up remains essential to determine the durability of the hematologic response and assess growth, neurodevelopment, and potential treatment-related complications. Molecular testing, when available, may further clarify the diagnosis and permit genotype-phenotype correlation.

Overall, this case contributes to the documented neonatal spectrum of DBA and illustrates the value of individualized diagnostic and therapeutic decision-making supported by longitudinal surveillance.

# Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Henrique de Liz Arcari

**Acquisition, analysis, or interpretation of data:** Henrique de Liz Arcari

**Drafting of the manuscript:** Henrique de Liz Arcari

**Critical review of the manuscript for important intellectual content:** Henrique de Liz Arcari

## Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## Acknowledgements

All data and study materials are available on reasonable request (harcari99@gmail.com). Figures 2 and 3 were created using Perplexity (Perplexity AI, Inc., CA, USA) based on the clinical data provided by the author. The figures were subsequently reviewed and validated before submission.

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