Annals of Clinical Case Reports

Case Report
Published: Dec 16, 2025

Incidental Discovery of a Rare Hemoglobin Variant (Hb G-Siriraj) in a Moroccan Patient During HbA1c Measurement by Capillary Technique

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Abstract

Background: Hemoglobin G-Siriraj is a rare hemoglobin variant resulting from a point mutation in the β-globin gene (HBB: c.22G>A), generally asymptomatic in its heterozygous state. We report here the second suspected case identified in Morocco, discovered incidentally during routine HbA1c testing using capillary electrophoresis.

Methods: The variant was identified in a 58-year-old Moroccan patient undergoing biological follow-up for cardiovascular risk. An abnormal peak was observed during HbA1c measurement on the Capillarys OCTA 3 Sebia® analyzer. Additional investigations using high-performance liquid chromatography (ARKRAY), alkaline capillary electrophoresis, and acid agarose electrophoresis suggested the presence of Hb G-Siriraj. The HbA1c result was not affected by the variant, allowing a reliable interpretation. Definitive diagnosis requires molecular analysis of the HBB gene.

Conclusion: This case illustrates the analytical contribution of modern diagnostic platforms in identifying rare hemoglobin variants. It emphasizes the importance of integrating multiple analytical techniques and post-analytical interpretation to ensure accurate diagnosis and result validation.

Keywords: Hemoglobinopathy; capillary electrophoresis; Hb G-Siriraj; HbA1c

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Received Date: *03 Dec 2025*
Accepted Date: *15 Dec 2025*
Published Date: *16 Dec 2025*

Citation:
Rifi W, Benlamkaddem T, Eddair Y, Biaz A, Bouhsain S, Dami A, et al. Incidental Discovery of a Rare Hemoglobin Variant (Hb G-Siriraj) in a Moroccan Patient During HbA1c Measurement by Capillary Technique. Ann Clin Case Rep. 2025; 10: 2805.
***ISSN: 2474-1655**.*

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Introduction

The measurement of glycated hemoglobin (HbA1c) has become a cornerstone in the monitoring of diabetes [1]. However, this routine biochemical analysis can sometimes unexpectedly reveal hematological abnormalities, including rare hemoglobin variants. These incidental findings underscore the growing role of the laboratory in detecting genetic pathologies that are often clinically silent [2,3].

Hemoglobin variants result from point mutations affecting the genes encoding globin chains. Although some are well-described, others remain exceptional and poorly understood, making their identification challenging, especially when they interfere with common tests like HbA1c [4].

Improvements in analytical techniques, particularly with the emergence of state-of-the-art analyzers like the Capillarys OCTA 3 (Sebia®), offer better resolution of chromatographic and electrophoretic profiles. This tool not only allows for the detection of suspicious anomalies during HbA1c measurement but also enables their further investigation via capillary electrophoresis in hemoglobin mode [5].

In this work, we report a case of a rare hemoglobin variant identified through coupled analysis on the Capillarys OCTA 3 (Sebia®). This case illustrates the contribution of capillary electrophoresis in revealing and rapidly characterizing atypical hemoglobinopathies in a clinical context where they could easily go unnoticed.

Case Presentation and Results

Mrs. S.M., a 58-year-old woman followed for hypertension and dyslipidemia, underwent a biological workup prescribed by her cardiologist during a routine consultation. The complete blood count was unremarkable, with hemoglobin at 12.5 g/dL and a red blood cell count of $4.39 \times 10^6/\mu L$, without morphological abnormalities. The iron status showed a ferritin level of 47 ng/mL, indicating sufficient iron stores. Fasting blood glucose was 0.98 g/L, and lipid and renal profiles were within normal limits.

Table 1: Summary of the analytical techniques used.

Technique	Principle	Main Result	Interpretation
Capillarys OCTA 3 – HbA1c Mode	Capillary electrophoresis in alkaline buffer	HbA1c: 5.4%; abnormal peak representing 33.5% of total Hb, migrating in zone 180–200	Atypical profile; suspicion of a hemoglobin variant.
Capillarys OCTA 3 – Hemoglobin Mode	Capillary electrophoresis in alkaline buffer	Variant migrating in Hb D zone at 35.4%; Hb A: 60.9%; Hb A2: 3.3%	
HPLC – ARKRAY ADAMS A1c HA-8180V®	High-performance liquid chromatography	HbA1c: 5.2%; presence of a variant interpreted as Hb C by the analyzer	Possible co-elution; identified as Hb C
Acid Gel Electrophoresis	Agarose gel electrophoresis in acidic medium	Migration of the variant in the zone corresponding to Hb C	Mobility identical to that of Hb C

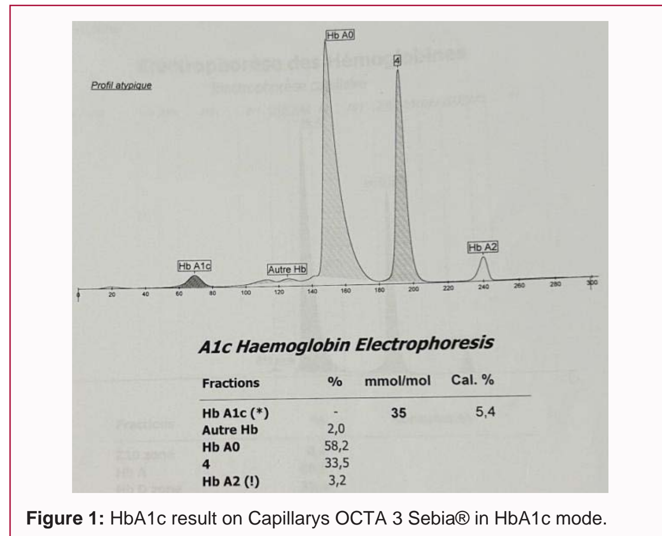

Figure 1: HbA1c result on Capillarys OCTA 3 Sebia® in HbA1c mode.

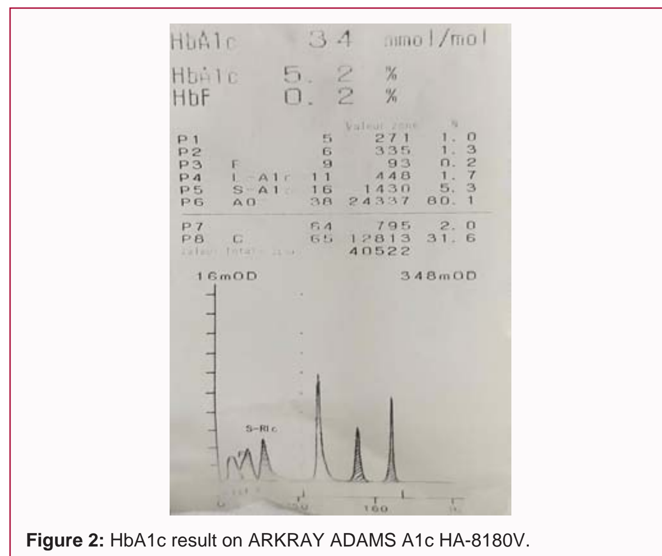

Figure 2: HbA1c result on ARKRAY ADAMS A1c HA-8180V.

The glycated hemoglobin (HbA1c) measurement, initially performed on the Capillarys OCTA 3 (Sebia, France) analyzer in HbA1c mode, revealed a value of 5.4%. This analysis also revealed an atypical electrophoretic profile, marked by the presence of an abnormal peak representing 33.5% of the total hemoglobin, migrating in a non-referenced zone, between 180 and 200, outside the standard identification windows for HbA, HbA2, HbF, HbC, or HbS fractions (Figure 1).

Given this anomaly, an HbA1c measurement was repeated using the HPLC method on the ARKRAY ADAMS A1c HA-8180V analyzer. This showed an HbA1c of 5.2%, slightly lower than that obtained by capillary electrophoresis, with the detection of a variant interpreted by the system as Hb C, based on its retention time (Figure 2).

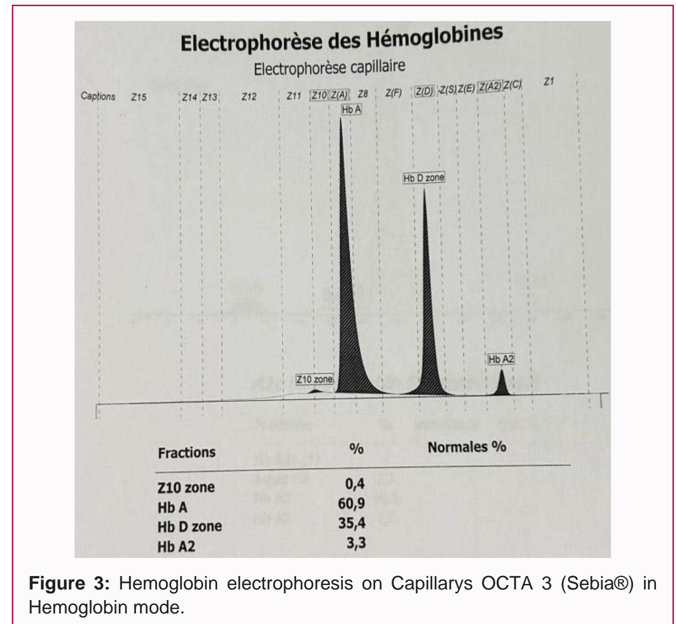

Figure 3: Hemoglobin electrophoresis on Capillarys OCTA 3 (Sebia®) in Hemoglobin mode.

Figure 4: Hemoglobin electrophoresis on agarose gel. a) Normal quality control. b) Migration of the studied hemoglobin variant in the Hb C zone. c) AFSC quality control.

To refine the characterization of the hemoglobin profile, alkaline capillary electrophoresis was subsequently performed on the same analyzer, in hemoglobin mode. The analysis revealed a peak migrating in the zone corresponding to Hb D, representing 35.4% of the total hemoglobin, associated with Hb A at 60.9% and Hb A2 at 3.3% (Figure 3). This migration pattern, incompatible with a classical hemoglobin, strongly suggests the presence of a rare structural variant.

Finally, acid agarose gel hemoglobin electrophoresis was performed for confirmation. This method, based on the differential migration of hemoglobins in an acidic medium, showed the variant migrating in the Hb C zone, consistent with the results obtained by HPLC. However, this apparent concordance likely masks an electrophoretic co-migration, a phenomenon frequently observed with certain rare variants like Hb G-Siriraj, known to mimic the migration of Hb C in an acidic medium while displaying a distinct profile under alkaline conditions (Figure 4).

Discussion

Hemoglobinopathies constitute a group of genetic diseases related to structural or functional abnormalities of globin chains. The Hb G-Siriraj variant, resulting from a point mutation in the HBB gene (c.22G>A), leads to a substitution of glutamic acid for lysine at position β7 [6]. Rarely encountered, this variant is generally asymptomatic in the heterozygous state; carrier subjects typically present with a normal CBC, without morphological abnormalities of red blood cells or signs of hemolysis.

The Hb G-Siriraj variant, although rare, was previously identified in Morocco by Ousguine et al. in a patient whose HbA1c measurement by HPLC (ARKRAY ADAMS HA-8180V) had initially interpreted the presence of a variant as Hb C [6]. Electrophoresis performed in hemoglobin mode on the Capillarys specified a migration in the D zone, supporting a G-Siriraj type variant. This migratory behavior has also been described in other contexts. Guan et al. reported a case of double heterozygosity combining Hb G-Siriraj and α-thalassemia, the analysis of which had mistakenly raised suspicion of β-thalassemia due to a falsely interpreted elevation of HbA2 [10]. A screening study conducted by Chen et al. identified a single case of Hb G-Siriraj among over 23,000 subjects analyzed by capillary electrophoresis, confirming the possibility of detection even at very low prevalence [11]. Finally, Olivieri et al. showed that the Capillarys in HbA1c mode allowed visual detection of abnormal profiles in more than 80% of tested variants, even without automatic identification [12]. In contrast, the homozygous expression of Hb G-Siriraj is likely to alter red blood cell physiology. One mechanism involved is cellular dehydration secondary to abnormal activation of the K-Cl cotransporter [7]. These ionic disturbances result hematologically in a characteristic hypochromic microcytic anemia, also observed in other structural variants like Hb C or Hb SC [8]. Cytological abnormalities such as target cells or the presence of Heinz bodies have also been described in homozygous or composite forms [9]. It is fundamental to emphasize that these biological manifestations remain, in the vast majority of cases, without notable clinical translation, which can delay diagnosis in the absence of thorough hematological investigations [10]. In our case, the initial suspicion occurred incidentally during the HbA1c measurement on the Capillarys OCTA 3 (Sebia®) analyzer, thanks to the observation of an abnormal peak migrating outside the standard windows. This early detection illustrates the value of this analyzer, capable of offering dual analysis in HbA1c mode and hemoglobin mode. To elucidate the nature of the variant, a complementary approach was undertaken, combining HPLC (ARKRAY), alkaline capillary electrophoresis, and acid gel electrophoresis.

The migratory profile observed in our case, characterized by a fraction of approximately 33–35% migrating in the D zone on capillary electrophoresis, as well as an apparent co-migration with Hb C on HPLC, points towards a structural variant of the G or D type. Among the hemoglobins migrating in the D zone, several differential diagnoses must be considered: Hb D-Punjab (or D-Los Angeles), Hb G-Philadelphia, Hb G-Coushatta, or Hb G-Siriraj [2-4]. The absence of evocative clinical signs, hematological disorders, or significant abnormalities in the blood count rules out symptomatic forms such as homozygous or composite D hemoglobinopathies. Hb D-Punjab, although migrating in the D zone, generally presents a higher percentage in heterozygosity and is sometimes accompanied by moderate microcytosis. Hb G-Philadelphia also migrates in this zone, but its percentage is often slightly lower, and it is more frequently encountered in certain Central Asian populations. In contrast, Hb G-Siriraj is characterized by a substitution at position β7 (Glu→Lys) and is distinguished by a constant migration in the D zone in alkaline capillary electrophoresis, a mobility similar to that of Hb C in acid phase, and a near-absence of clinical or biological repercussion [6,10,11]. The profile observed in our case (normal Hb, absence of anemia, normal ferritin, fraction of ~33–35%, co-migration with Hb C on HPLC, migration in D zone on capillary, silent behavior) is therefore compatible with that of a heterozygous carrier of Hb G-Siriraj as described in the literature.

Definitive confirmation of this diagnosis, however, relies on molecular analysis of the β-globin gene to identify the causative HBB:c.22G>A mutation.

The Capillarys OCTA 3 Sebia® is based on the principle of capillary electrophoresis in an alkaline medium, where different hemoglobin fractions are separated based on their electrical charge in a specific buffer within silica capillaries. In HbA1c mode, the analyzer distinguishes glycated hemoglobin (HbA1c) from non-glycated hemoglobin (HbA0) by their differential migration, then automatically calculates the HbA1c proportion using the formula: HbA1c (%) = (area of the HbA1c fraction) / (total area of HbA0 + HbA1c fractions) × 100 [5]. In our case, although the presence of the variant was revealed fortuitously by an atypical peak on the electrophoretic profile, no interference was observed in the separation of the HbA0 and HbA1c fractions. Thus, the obtained value can be considered reliable, validated, and reported to the clinician without reservation. For this patient, an explanatory comment was added to the report:

"Presence of a heterozygous hemoglobin variant. The thresholds used for the diagnosis and monitoring of diabetes mellitus cannot be used. The patient is their own control." In contrast, in some cases, hemoglobin variants can migrate in a way that overlaps with HbA1c or HbA0, thus disrupting the calculation of the glycated fraction. Variants such as Hb La Désirade or Hb Novara are known examples, their electrophoretic behavior inducing co-migration with the fractions used for calculation. This phenomenon can lead to an overestimation or underestimation of the measured value, making the result unreliable [9]. In these situations, the HbA1c value must not be reported, and a clear comment must accompany the report:

"The HbA1c level cannot be reported due to the presence of a hemoglobin variant that interferes with its calculation. It is recommended to use another marker for glycemic monitoring (fructosamine, glycemic profile)." This approach ensures clear communication with the clinician and prevents any misinterpretation that could impact patient management.

Conclusion

This case highlights the importance of the laboratory's role in

detecting hemoglobin variants, even outside of an obvious clinical context. The complementarity of analytical techniques, particularly capillary electrophoresis on the Capillarys OCTA 3, combined with HPLC and acid electrophoresis, allows for effective identification and characterization of atypical hemoglobins. In a routine context, the recognition of these abnormal profiles can prevent interpretation errors, particularly in the context of glycemic monitoring. Molecular confirmation remains necessary for a definitive diagnosis and to enrich the knowledge of rare variants in understudied populations.

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