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CASE REPORT

Graves' Disease: Acquired Cause of a Moderate Increase in Hemoglobin A2 Level

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SUMMARY

Background: **Hyperthyroidism can lead to diverse hematological disorders, such as microcytosis and a mild increase in hemoglobin A2 fraction.**
Methods: **This study reported a 31-year-old woman of Moroccan origin recently diagnosed with Graves' disease. Her blood tests revealed microcytosis, hypochromia, and a normal ferritin level. A phenotypic analysis of hemoglobin was performed using two techniques: capillary electrophoresis and reversed-phase high performance liquid chromatography.**
Results: **Both techniques indicated a slight increase in hemoglobin A2 level. These results initially suggested heterozygous beta-thalassemia, eventually correlating with the concurrent presence of Graves' disease, as evidenced by the normalization of hemoglobin A2 level following treatment.**
Conclusions: **This case highlights the importance of having clinical, biological, and therapeutic data for a relevant interpretation of a phenotypic hemoglobin study.**
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KEYWORDS

Graves' disease, hyperthyroidism, phenotypic hemoglobin study, moderate increase in hemoglobin A2, heterozygous beta-thalassemia, euthyroidism

INTRODUCTION

Graves' disease is an autoimmune disorder caused by TSH receptor-stimulating antibodies, often associated with anti-thyroid peroxidase antibodies and less frequently with anti-thyroglobulin antibodies. It predominantly affects women and is the most common cause of hyperthyroidism [1].
Hyperthyroidism can cause various hematological disorders, including microcytosis and slight elevations in hemoglobin A2 (HbA2). Consequently, it may imitate a beta-thalassemic trait, potentially leading to a misinterpretation of the results.
We present a case of an acquired increase in HbA2 levels identified in the context of a recent diagnosis of

Graves' disease.

CASE REPORT

This is a 31-year-old Moroccan woman with no notable medical history, in whom the diagnosis of Graves' disease has been confirmed. At the moment of diagnosis, thyroid function tests revealed (Chemiluminescence technique on Alinity®): Ultrasensitive TSH < 0.01 mUI/L (normal 0.4 - 4 mUI/L), Free thyroxine (FT4) 2.91 ng/dL (normal 0.7 - 1.48 ng/dL), Free tri-iodothyronine (FT3) 5.78 pg/mL (normal 1.71 - 3.71 pg/mL), anti-thyroid peroxidase antibody 539.71 UI/mL (normal < 5.61 UI/mL) and anti-thyroglobulin antibody 57 UI/mL (normal 0.2 - 4.11 U/mL).

Blood tests showed microcytosis and hypochromia without anemia (Beckmann Coulter DxH900®): hemoglobin 13.1 g/dL (normal 12 - 16 g/dL), mean corpuscular volume 74.2 fL (normal 82 - 98 fL), mean corpuscular hemoglobin 24.9 pg (normal ≥ 27 pg) and red blood cell distribution width (RDW) 13.6% (normal 11 - 14.5%). The analysis of red blood cell morphology on a blood smear did not reveal any abnormalities.

Moreover, serum ferritin was within the normal range at 35 ng/mL (normal 11 - 306.8 ng/mL), and CRP was negative at 1 mg/L (normal < 5 mg/L).

Given the isolated microcytosis and normal iron status, a beta-thalassemic trait was suspected. A phenotypic study of hemoglobin was requested.

The hemoglobin analysis revealed a moderate increase in hemoglobin A2 fraction (Figures 1 and 2) both in capillary electrophoresis (Capillarys 2 Flex piercing, Sebia®) and thalassemia mode reversed-phase high performance liquid chromatography analyzer (RP-HPLC, ADAMS A1c HA-8180T, Arkray®). The standard values reported in the literature for the HbA2 fraction range between 2.2% and 3.4% [2].

Considering all these results, the interpretation of the hemoglobin study becomes intricate for this patient: Could the increase in HbA2 be related to a genetic factor (heterozygous beta-thalassemia) or an acquired condition (hyperthyroidism)?

The patient was treated with carbimazole (20 mg/day) and propranolol (40 mg/day). She tolerated the antithyroid drug well, with no neutropenia during the first month: Hb 13.8 g/dL, MCV 75.8 fL, MCH 25 pg, RDW 14.2%, WBC 16 G/L, neutrophils 10.5 G/L, and platelets 420 G/L. The treatment was therefore continued regularly.

Eight months later, the patient was clinically and biochemically euthyroid: FT4 1.02 ng/dL and FT3 2.76 pg/mL. The evolution of the HbA2 level on both capillary electrophoresis (Figure 3) and RP-HPLC (Figure 4) is marked by its normalization confirming the acquired origin of the moderate increase in HbA2.

DISCUSSION

This case draws attention to the hematological abnormalities that occur during hyperthyroidism and may be misinterpreted by the biologist as beta-thalassemia trait. Although Mediterranean origin, microcytosis (without iron deficiency), hypochromia, and an increase in hemoglobin A2 were suggestive of heterozygous beta-thalassemia, some elements did not support this diagnosis:

1) The increase in HbA2 in our patient does not align with the values typically observed in heterozygous beta-thalassemia (usually > 4.5 - 5%) [3].

2) The absence of red cell morphological disorders. Indeed, individuals with a beta-thalassemic trait typically show more pronounced microcytosis and hypochromia than what was observed in our patient [3], and the blood smear generally reveals anisopoikilocytosis (elliptocytes, dacryocytes).

In our case, the increase in HbA2 was ultimately attributed to the context of hyperthyroidism associated with Graves' disease, as evidenced by its normalization after treatment. The French Society of Clinical Biology (SFBC) has clarified that a sole elevation of HbA2 is not always indicative of a beta-thalassemic trait. It can also be observed in various situations, including antiretroviral treatment, hyperthyroidism, and vitamin B12 or folat deficiencies [4].

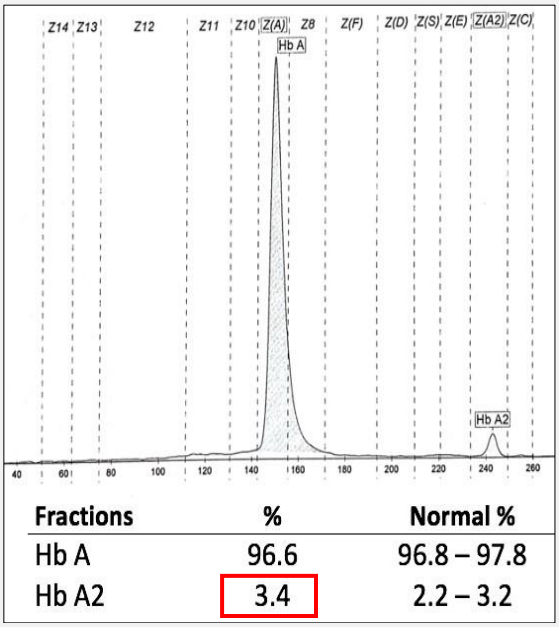
Several studies have shown that thyroid status influences the HbA2 level [5-8]. Kuhn JM & al.'s study revealed a statistically significant increase ($p < 0.001$) in the average HbA2 level in untreated hyperthyroid patients compared to a group that achieved euthyroidism after treatment [5]. In other studies [7,8], it was the genotypic study of globin chains that helped to exclude a constitutional origin for the increased HbA2. Unfortunately, in our case, these genotypic tests are not available.

Finally, the role of thyroid hormones in modulating the synthesis of globin chains is not well known. In a normal state, delta chain synthesis is relatively more active in very young precursors, then decreases during the final stages of erythroid maturation [9]. Thyroid hormones could directly enhance erythropoiesis by inducing accelerated maturation of red blood cells. Hyperthyroidism can therefore be responsible for the increased HbA2 levels.

CONCLUSION

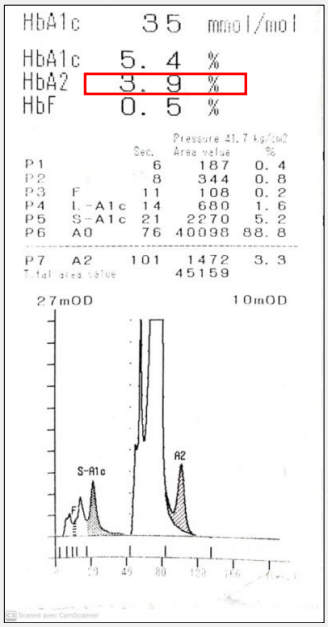
Hyperthyroidism is an acquired cause of a moderate increase in HbA2 levels. Our case perfectly illustrates the necessity of having clinical, biological, and therapeutic data for a relevant interpretation of a phenotypic hemoglobin study.

1



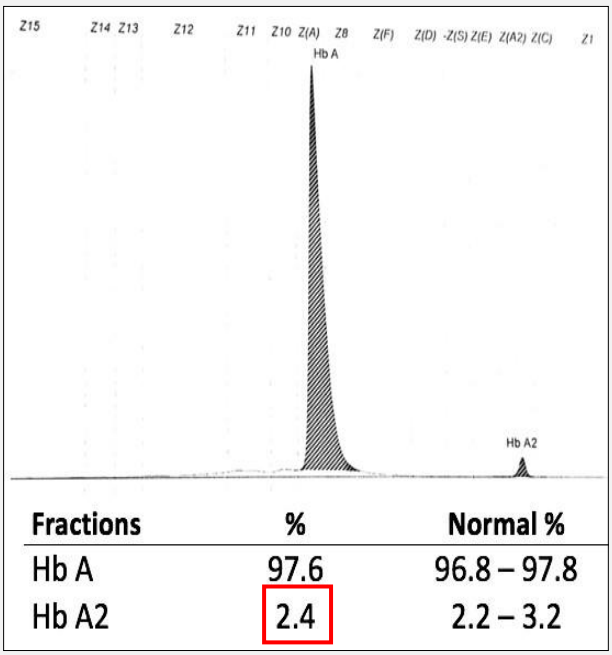
Fractions	%	Normal %
Hb A	96.6	96.8 – 97.8
Hb A2	3.4	2.2 – 3.2

2



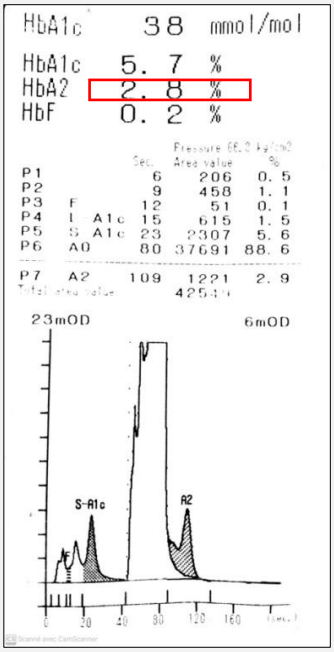
Figures 1 & 2. Results of the phenotypic hemoglobin study using capillary electrophoresis (Figure 1) and thalassemia mode RP-HPLC (Figure 2), conducted before treatment (hyperthyroidism phase).

3



Fractions	%	Normal %
Hb A	97.6	96.8 – 97.8
Hb A2	2.4	2.2 – 3.2

4



Figures 3 & 4. Results of the phenotypic hemoglobin study using capillary electrophoresis (Figure 3) and thalassemia mode RP-HPLC (Figure 4), conducted 8 months after treatment (euthyroid phase).

Publication Ethics:
The article is produced ethically and responsibly, with no fabrication or falsification of data, no plagiarism and no manipulation of images.

Declaration of Interest:
The authors declare that they have no conflicts of interest.

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