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CASE REPORT

Coffee Colored Plasma: Which Interference Should be Considered?

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SUMMARY

Background: **An icteric coloration or lipemic appearance of serum is frequently observed in clinical practice. These changes in appearance can be detected either visually after centrifugation or during the analytical phase by spectrophotometric determination of the HIL indices (hemolysis, icterus, lipemia). These endogenous interferences can be the cause of analytical interferences affecting the accuracy of the results of the analyses carried out.**
Methods and Results: **Our observation describes an atypical brown 'coffee-like' coloration of the plasma, causing a discrepancy between the total bilirubin dosed and the icterus index measured on our analytical system.**
Conclusions: **It is essential to preserve the crucial information gathered during the pre-analytical and analytical phases, in order to avoid improperly cancelling the results or giving incorrect results as a result of analytical interference.**
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KEYWORDS

brown plasma, Eltrombopag, icterus index, interference, macroscopic examination

INTRODUCTION

Modification of the colorimetric appearance, viscosity or turbidimetry of blood samples can cause interferences that can impact the accuracy of the results of the biological examinations rendered. These changes in the appearance of the serum can be detected either during the pre-analytical phase by macroscopic examination of the sample after centrifugation or during the analytical phase by spectrophotometric determination of the HIL indices (Hemolysis, Icterus, Lipemia). Our observation describes an atypical brown "coffee-looking" coloration of the plasma at the origin of a discrepancy between the total bilirubin dosed and the icterus index measured on our analytical system.

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Table 1. Biochemical assay results.

Parameters	Results	Reference value
Serum appearance	Clear	-
Hemolysis index	0	-
Icterus index	1+	-
Total bilirubin (µmol/L)	17.1	3.4 - 20.5
Direct bilirubin (µmol/L)	6.84	0.0 - 8.6
Creatine kinase (IU/L)	22	24 - 195
Lactate dehydrogenase (IU/L)	138	125 - 243
Aspartate aminotransferase (IU/L)	14	< 35
Alanine aminotransferase (IU/L)	16	< 40
Haptoglobin (g/L)	2.09	0.14 - 2.58

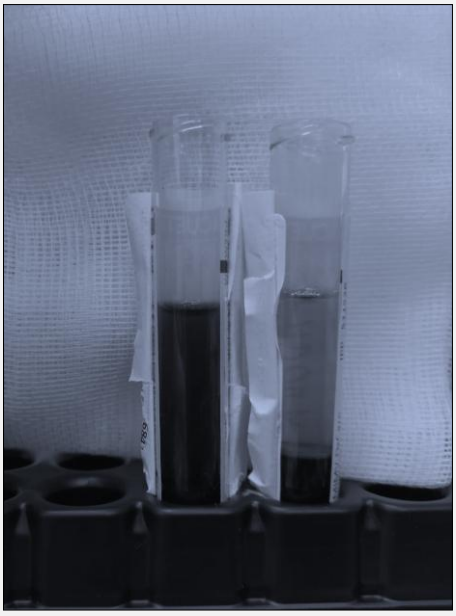

Figure 1. A Plasma of our patient, B Control plasma.

CASE REPORT

This is a 27-year-old patient with severe idiopathic aplastic anemia and a candidate for allogeneic hematopoietic stem cell transplantation. She was hospitalized in emergency for the management of a hemorrhagic syndrome. A biological blood test was requested urgently. After centrifugation, the plasma showed an atypical dark brown color (Figure 1).

Such an appearance is suggestive of hemolytic anemia, rhabdomyolysis or methemoglobinemia. The HIL test performed in parallel with the biomarker assay on the Alinity ci-series Abbott® analyzer showed no hemolysis or lipemia, but an icterus index equal to 1+ (corresponding to a total bilirubin concentration between 34 and 67 µmol/L). This is in contrast to a normal total bilirubin level of 17.1 µmol/L and a normal liver test (Table 1). In addition, the normality of lactate dehydrogenase (LDH), haptoglobin and creatine kinase (CK) levels exclude intravascular hemolysis and rhabdomyoly-

sis.
After communication with the clinician, the possibility of an iatrogenic etiology is suspected due to the patient's intake of Eltrombopag at a high dose (150 mg/24 hour), a drug approved for the treatment of severe aplastic anemia (SAA).

DISCUSSION

According to the literature, the possible causes of a brown plasma coloration may be related to the presence of high levels of metalbumin, myoglobin or methemoglobin linked, respectively, to hemolytic anemia, rhabdomyolysis or exposure to exogenous oxidizing agents [1,2]. In order to exclude these pathologies, we sequentially added LDH and haptoglobin for the evaluation of intravascular hemolysis, as well as CK for the study of rhabdomyolysis. Measurement of methemoglobin by co-oximetry could not be performed. The results obtained exclude rhabdomyolysis (normal CK and LDH) as well as intravascular hemolysis (normal haptoglobin). The clinico-biological discussion raised the possibility of an adverse effect related to the patient's intake of high doses of Eltrombopag. It is a non-peptide thrombopoietin receptor agonist, approved for the treatment of SAA, idiopathic thrombocytopenic purpura, and chronic thrombocytopenia associated with hepatitis C [3]. In SAA, high doses (150 mg/24 hour) may be used compared to other approved uses [2], which could result in major drug exposure and a larger and more severe number of adverse reactions. Brownish coloration of the plasma (serum) sometimes associated with hyperpigmentation is thus reported on the Eltrombopag technical sheet as an infrequent adverse effect [4] and reversible upon discontinuation of treatment. A review of the literature allowed us to find a few cases of patients on high doses of Eltrombopag [2,5-7] and who presented the same coffee coloring of their serum.
On the other hand, this drug, metabolized and eliminated by the liver, is known for its hepatotoxicity justifying regular monitoring of the liver test [6]. In our patient, the normal level of total bilirubin (Diazo method, Abbott Alinity®) is discordant with an icterus index corresponding to 34 - 67 µmol/L of total bilirubin. The normality of the liver test raises the possibility of analytical interference of Eltrombopag on the determination of bilirubin. Rojas et al. reported the same variation in a patient with SAA treated with Eltrombopag 150 mg/24 hour with a total bilirubin level of 20.5 µmol/L (Diazo method, Abbott Alinity®) and a discordant icterus index [2]. The total bilirubin assay was checked in another laboratory using the high-performance liquid chromatography (HPLC) technique. The result, similar to that obtained by diazoreaction (17 µmol/L), excludes any analytical interference of Eltrombopag on the determination of bilirubin by the Alinity Abbott® system [2]. Other studies have evaluated this interference and have shown a variety of results ranging from negative interference, no interference, to positive interference. These variations appear to be due to several factors, including the pH of the sample, the analyzer used, and the concentration of the drug being studied [3].

CONCLUSION

Our observation illustrates the importance, of contextualized interpretation of biomarkers and clinicobiological discussion in cases of abnormal serum or plasma coloration. This approach would avoid an abusive cancellation of the assessment or an erroneous return of results following analytical interference, thus ensuring optimal patient care.

Declaration of Interest:
None.

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