INTERFERENCE OF DAPSONE IN HBA$_1$C MONITORING OF A DIABETIC PATIENT WITH POLYCHONDРИTIS

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We report the case of a 80-year-old man treated with Dapsone (4,4'-diaminodiphenyl sulfone) for relapsing polychondritis. During the follow-up, diabetes mellitus appeared. Fasting glycemia remained high, but surprisingly HbA$_1$c remained in the normal range. This unusual phenomenon is discussed.

CASE REPORT

A 80-year-old man was regularly surveyed in our service since 1987 for a relapsing polychondritis and treated with Dapsone, 100 mg per day, with a good outcome on chondritis.

During the follow-up, a prostate carcinoma was diagnosed in 1990 and treated with surgery and brachytherapy. An in situ bladder carcinoma was treated in 1997 with BCG therapy. Both carcinomas were regularly surveyed and remained controlled: PSA was < 0.5 ng/mL (N < 4), periodic bladder cytologies showed no malignant cells.

Biological survey showed a normal red blood cell count with a mild hemolysis [bilirubin = 35 mMol/L (0 < N < 17), LDH = 350 UI/L (150 < N < 320) and reticulocytosis 155 × 10$^9$/L] due to a chronic Dapsone-induced methemoglobinemia which was evaluated around 2%.

In 1999, fasting glycemia was controlled several times around 1.3 g/L (7.4 mMol/L) checked on 100 UI/mL and 30UI/mL lithium heparinate test-tubes. Fasting insulinemia was normal at 6 mMol/L (4 < N < 6) and HbA$_1$c was in the normal range: 4.2% (N < 6.5%). Proteinuria was about 0.23 g/24 h and albuminuria around 58 mg/24 h (microalbuminuria). Diet was proposed and compliance was good during two years.

At the last visit in January 2002, he complained of polydipsia, polyuria and weight loss. Fasting glycemia was 1.7 g/L (9.5 mMol/L). Several fasting glycemia were controlled per 24 hours. At 7 AM fasting glycemia was 1.93 g/L (10.7 mMol/L). At 10 AM 2.07 g/L (11.5 mMol/L). At 15 PM fasting glycemia was 2.52 g/L (14.9 mMol/L). At 18 PM fasting glycemia was 2.07 g/L (11.5 mMol/L). Glycated hemoglobin (HbA$_1$c) was still normal: 4%. Insulinemia and plasma level of peptide C were also normal. Faced with such features, antidiabetic treatment with acarbose (Glucort®) was begun with a good outcome on clinical symptoms and glycemia. Since then, evaluation of long-standing glycemic control was based on fructosamine concentration and remained correct.

DISCUSSION

In our case, Dapsone (4,4'-diaminodiphenyl sulfone), an anti mycobacterium leprae and immunomodulatory agent was used to control a relapsing polychondritis with a good outcome on inflammation in an 80-year-old patient. Treatment tolerance was acceptable with a low level of dapsone-induced methemoglobinemia and hemolysis. During the follow-up, diabetes mellitus appeared. Fasting glycemia was controlled several times with different methods and remained high, since surprisingly HbA$_1$c remained in the normal range.

Methemoglobin is hemoglobin in which the iron has been oxidized ($\alpha_2^+$ $\beta^+$). This oxidized hemoglobin is no longer capable of reversibly binding oxygen and may be induced by dapsone treatment.
Four minor fractions of HbA called HbA$_{1a1}$, HbA$_{1a2}$, HbA$_{1b}$, HbA$_{1c}$ have been separated by Allen, using red cell hemolysat chromatography [1]. HbA$_{1c}$ may represent 5% of the total hemoglobin. These hemoglobins are progressively produced in circulating red blood cells during their 120 days life span. HbA$_{1a1}$ and HbA$_{1a2}$ respectively contain fructose 1-6 bisphosphate and glucose-6 phosphate fixed on N-terminal valin of beta chain. HbA$_{1c}$ contains glucose fixed in the same way. This fixation between reductive function in 1 of glucose and the NH$_2$ of valin requires Amadori rearrangement [1]. It is non-enzymatic and unreversible. Glucose level increases with red blood cell aging and is proportional to glucose concentration. In diabetes mellitus, HbA$_{1c}$ may rise until 15% and evaluation of this glycated hemoglobin is used to evaluate long-standing glycemic control as recommended by Diabetes Consensus Development Conference [2]. As red cell life time is about 120 days, HbA$_{1c}$ reflects the glycemic state of the past three months. Responsiveness of dapson in lowering HbA$_{1c}$ percentage has been shown in NOD mice [3]. Such an effect on HbA$_{1c}$ can be secondary to hemolysis induced by N-hydroxy metabolites of dapson responsive to hemolytic activity of dapson [4] as in our observation. Thus dapson affects the life span of erythrocytes and HbA$_{1c}$ level. The fall in HbA$_{1c}$ concentration is explained by increased erythrocytopoiese as a product of drug-induced hemolysis [5]. Plasma fructosamine concentration is another method for evaluating intermediate-standing glycemic control and is not affected by hemolysis. So our case recalls that in patients presenting chronic hemolysis such as those treated with Dapsone, HbA$_{1c}$ evaluation gives false low level and fructosamine evaluation may be preferred to estimate glycemic control.

REFERENCES

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