IMAJ • VOL 13 • JULY 2011

Metformin-Induced Hemolytic Anemia

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KEY WORDS: hemolytic anemia, glucose 6-phosphate dehydrogenase (G6PD) deficiency, diabetes, metformin

IMAJ 2011; 13: 444–445

Glucose 6-phosphate dehydrogenase deficiency is an X-linked inherited disorder that increases the vulnerability of erythrocytes to oxidative stress. It is the most common enzyme deficiency worldwide, and usually affects persons from African, Asian, Mediterranean or Middle Eastern descent. Different gene mutations cause different levels of enzyme deficiency [1]. Complications include hemolysis and neonatal jaundice.

We describe a young man with new-onset diabetes mellitus type II who was started on metformin. Within a few days he developed jaundice and was admitted for investigation.

PATIENT DESCRIPTION

A 29 year old man of North African Jewish descent was admitted to the Department of Medicine because of weakness and jaundice that had begun a week earlier, becoming progressively more severe until his admission. Two weeks previously he had been diagnosed with diabetes and was put on a low sugar diet together with metformin 850 mg 3 times daily. He denied recent infections, taking other medications, previous liver disease or blood transfusion, any surgical or dental treatment; and apart from weakness and the progressive jaundice he felt quite healthy. Physical examination was unremarkable except for icterus in the sclera.

Blood smear showed hemoglobin of 8.7/dl (2.7 x 10^6 red blood cells/mm^3 with reticulocytosis of 12%), mean corpuscular volume 93.4 fl, mean corpuscular hemoglobin 31.9 pg, 9120 leukocytes/mm^3 and 277,000 thrombocytes/mm^3. Haptoglobin level was 13.2 mg/dl (very low). Coombs' test was negative. Lactate dehydrogenase was 524 u/L, iron 106 µg/dl, bilirubin total 3.50 mg/dl (direct 0.90 mg/dl), albumin 4.20 g/dl and globulin 3.10 g/dl, aspartate aminotransferase 72 u/L and alanine aminotransferase 140 u/L (all liver enzymes returned to normal levels within 3 days). Alkaline phosphatase was normal, as were other electrolytes and kidney function tests. Tests for hepatitis B and C were negative, and vitamin B12 and folic acid levels were normal. Thyroid function tests and coagulation tests (international normalized ratio 1, partial thromboplastin time 26 seconds) were normal. The blood differential count showed mild anisocytosis, mild basophilic stippling, and polychromasia. Lipid profile was normal. Electrocardiogram, chest X-ray, and chest and abdominal computed tomography were all normal.

Metformin was discontinued. The jaundice gradually disappeared and the serum bilirubin concentration and all other elevated liver enzymes decreased to normal. Hemoglobin level increased from 8.7 to 9.4 g/dl without the need for packed red blood cells. Glucose 6-phosphate dehydrogenase level was low (below 3 IU/g Hb, normal > 4.5 IU/g Hb).

COMMENT

We describe a young man who was recently diagnosed with diabetes mellitus type II and was treated with metformin; he subsequently developed severe Coombs'-negative hemolytic anemia. We believe that this intravascular hemolysis was due to a genetic trait, G6PD deficiency (of which he was unaware), and that the new medication (metformin) caused an oxidative stress that led to the hemolytic anemia. After discontinuation of the drug the hemolysis abated and his hemoglobin level stabilized and gradually returned to normal.

In a G6PD-deficient subject hemolysis may occur as a result of infection or following ingestion of various drugs; and among diabetic patients it may be due to hypoglycemia [2], blood glucose normalization, ketoacidosis in the African but not the Mediterranean variant of G6PD deficiency [3], and following administration of metformin or glybenclamide [4].

The temporal relationship with metformin ingestion was quite strong in this patient, who noted symptoms within a few days of starting the metformin. In previous cases the time of onset of symptoms ranged from 9 to 14 days after starting metformin, and none resulted in massive hemolysis or death (all but one patient).

This case highlights the importance of clinical judgment and the possible association between a new medication and a new unusual clinical event. It emphasizes the importance of being open minded and looking for genetic mutations that could be part of the unexpected clinical phenomena that may appear during adolescence and adulthood.

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G6PD = glucose 6-phosphate dehydrogenase

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