Metformin-Induced Hemolytic Anemia

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G lucose 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
References

Capsule
Identification of the specific health-promoting factors made by probiotics
Despite aggressive marketing campaigns that highlight the beneficial effects of probiotics (therapeutics consisting of live microorganisms) on gastrointestinal health, in many cases the claimed benefits are made on the basis of limited or controversial clinical data. Moreover, there are far more hypotheses than experimental data on the molecular mechanisms by which probiotics alter gut homeostasis. A better understanding of these mechanisms could shed light on the disparate clinical data and perhaps even lead to more effective drugs that can substitute for living microbes. Studying Lactobacillus rhamnosus GG (LGG), which is used in yogurt as a nutritional supplement, Yan and team found that this bacterium secretes a soluble protein, called p40, which prevents death of intestinal epithelial cells through activation of the epidermal growth factor receptor signaling pathway. In three mouse models of intestinal inflammation, administration of recombinant p40 (encased within special hydrogel beads to minimize its degradation) reduced disease symptoms in both a therapeutic and preventive setting. Whether p40 alone will show similar activity in humans without adverse side effects remains to be seen, but these results support the idea that the identification of the specific health-promoting factors made by probiotics is an avenue worth exploring.

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Capsule
Tolerant TB due to efflux pumps
Eradication of human tuberculosis with antitubercular drugs has been challenged by emerging populations of resistant bacteria that had been thought to be quiescent. A new study shows that infection of macrophages by Mycobacterium species leads to the development of a replicating and metabolically active population of intracellular bacteria that are multidrug -olerant and can spread to other granuloma lesions. Using a zebrafish larval model infected with Mycobacterium marinum and cultured human macrophages infected with Mycobacterium tuberculosis, Adams and group show that dividing bacteria tolerant to multiple drugs arise within individual macrophages as well as within macrophages in granulomas. Bacterial efflux pumps induced by macrophages boosted bacterial growth and drug tolerance at early stages of tuberculosis infection, which persisted even after dissemination of the bacteria in the granuloma. Mutating the bacterial efflux pumps or treating the bacteria with pharmacological pump inhibitors reduced this macrophage-dependent drug tolerance and attenuated bacterial growth. These results argue in favor of using inhibitors of bacterial tolerance such as efflux pump inhibitors along with antimicrobial agents to halt Mycobacterium growth and eliminate residual resistant bacteria to shorten treatment times and avoid relapses in people with tuberculosis.

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“At least one way of measuring the freedom of any society is the amount of comedy that is permitted, and clearly a healthy society permits more satirical comment than a repressive, so that if comedy is to function in some way as a safety release then it must obviously deal with these taboo areas. This is part of the responsibility we accord our licensed jesters, that nothing be excused the searching light of comedy. If anything can survive the probe of humor it is clearly of value, and conversely all groups who claim immunity from laughter are claiming special privileges which should not be granted”

Eric Idle (b. 1943), English comedian, actor, author, singer, writer, and comedic composer who wrote and performed as a member of the popular British comedy group Monty Python