Jaundice From Diabetes Therapy

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In January 2013, a 41-year-old man presented for follow-up to our diabetes unit with jaundice, fatigue, dark urine, and stool discoloration. Four weeks earlier, he had suffered a sudden sensorineural hearing loss and was treated with a prednisolone taper scheme starting with 250 mg q.i.d. in addition to α-lipoic acid. Fasting hyperglycemia (274 mg/dL) was detected after initiation of the therapy. Further laboratory workup revealed a preexisting type 2 diabetes (HbA_{1c} 11.8% [105 mmol/mol], no GAD2 antibodies). Transaminases were normal. Insulin glargine and metformin 500 mg t.i.d. were initiated.

Upon follow-up, the patient reported that fatigue and yellow sclera manifested 4 days before. Thereafter, he stopped taking his medication. Physical examination was unremarkable except for jaundice. Total bilirubin was 18.1 mg/dL, aspartate aminotransferase 419 units/L, alanine aminotransferase 863 units/L, alkaline phosphatase 479 units/L, and γ-glutamyl transferase 2,181 units/L. Differential blood count was normal apart from mild eosinophilia (5.7%). The patient had no history of gastrointestinal disease, travel, or change of sexual partners. He denied excessive alcohol intake or the use of illicit drugs. Abdominal ultrasonography revealed hepatic steatosis. Mechanical cholestasis, portal vein thrombosis, Budd-Chiari syndrome, viral hepatitis, hemochromatosis, Wilson disease, and autoimmune hepatitis were excluded. A drug-induced hepatitis was suspected. Lymphocyte activation assay revealed activation (increased CD69 expression) of $CD4^+$ T cells and $CD19^+$ B cells after incubation with metformin (Fig. 1). Antibodies to metformin could not be detected.

As measures of hepatic synthetic function were normal and the patient was doing better after stopping metformin, watchful waiting was decided. Diabetes therapy was continued with insulin. Declining transaminases were observed as soon as the next day, but bilirubin increased until 10 days after the discontinuation of metformin. Pruritus and skin eruptions arose, and empirical treatment with ursodeoxycholic acid was started to accelerate bilirubin clearance. The symptoms subsided over the following weeks. Within 2 months, bilirubin and transaminase levels normalized. Eosinophils were still slightly elevated (4.1%). Reactivity of $CD4^+$ T cells

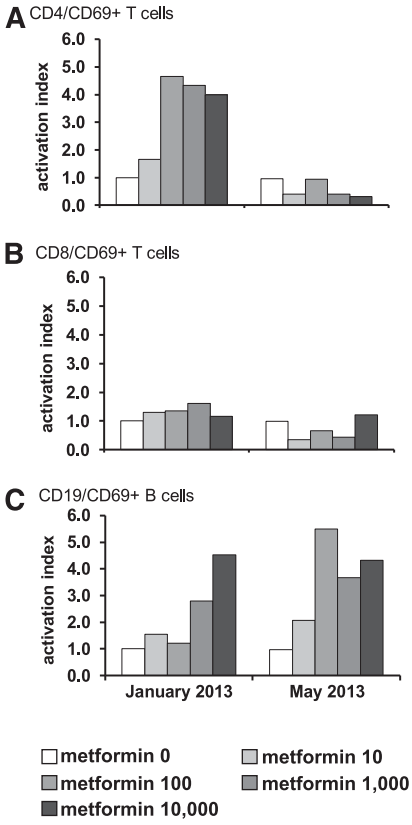

Figure 1—Dose-dependent effect of metformin on the activation (CD69 expression) of $CD4^+$ and $CD8^+$ T cells (*A*, *B*) and $CD19^+$ B cells (*C*) from a patient developing hepatocellular injury during metformin therapy. The figure shows the reactivity at time of acute manifestation and 4 months later. Peripheral blood mononuclear cells (PBMC) were isolated from 50 mL heparinized blood by standard methods; 5×10^5 PBMC were incubated with metformin at concentrations 0, 10, 100, 1,000 and 10,000 μg/mL for 24 h at 37°C, 5% CO_2 in a humidified atmosphere. Cell staining was performed using cocktails (Becton, Dickinson and Company, San Jose, CA) for the demonstration of activated (CD69-expressing) $CD4^+$ and $CD8^+$ T cells, $CD19^+$ B cells, and $CD56^+$ NK cells. Quadrants were set according to an isotype control. Results were expressed as an activation index dividing the percentage of CD69-expressing cells of the respective cell types with antigen exposure by that of CD69-expressing cells without antigen (metformin 0).

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toward metformin decreased, while that of $CD19^+$ B cells still persisted.

Only 13 cases of metformin-induced hepatitis have been described in the literature. Symptoms emerged 2–4 weeks after initiation of metformin and regressed after 3–12 weeks. In one case, the patient decided on his own to take a dose of 850 mg 6 weeks after he was free of complaints and within 24 h all symptoms reoccurred (1). In our case, the eosinophilia, rapid elevation of transaminases and their decrease after stopping the medication, skin eruptions, and former incrimination of metformin in similar cases made an idiosyncratic drug reaction probable. This was confirmed by the findings of the lymphocyte activation assay.

In all type 2 diabetes clinical guidelines, metformin is the first-line agent. Its use is growing because type 2 diabetes prevalence is on the rise, and metformin's contraindication with mild chronic renal failure is increasingly challenged (2). Furthermore, clinical trials are under way to evaluate its role in tumor prevention and therapy (3). Within this context, it is important to know about the rare adverse reactions.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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