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What's the diagnosis?

A 41-year-old male with type 2 diabetes mellitus taking dapagliflozin, one of sodium-glucose cotransporter-2 (SGLT2) inhibitors, 5 mg daily, was admitted to our hospital, with oliguric acute kidney injury. He reported no history of being exposed to IV contrast or other agents. Ultrasonography scans revealed no evidence of urinary tract obstruction, heart failure, or cirrhosis. Laboratory examination showed blood glucose of 74 mg/dL, hemoglobin A1c of 6.1 %, and serum creatinine of 3.0 mg/dL (baseline 1.1 mg/dL). Urinalysis was positive for glucose (+4) with osmolality of 836 mOsm/kg, and negative for protein, occult blood, crystals, or sediment abnormalities.

A histological preparation of kidney revealed focal isometric vacuolization in the proximal tubules (Figure 1) and pale periodic acid-Schiff (PAS)-positive glycogen accumulation within the cytoplasm of epithelial cells (Figure 2). Electron microscopy showed cytoplasmic vacuoles in the proximal tubules with preserved brush borders (Figure 3). A diagnosis of osmotic nephropathy, most likely due to dapagliflozin, was made. His physical status and serum creatinine level returned to normal after normal saline infusion and dapagliflozin discontinuation.

Osmotic nephropathy describes structural changes with vacuolization and swelling of the proximal tubules that obstruct urine flow, resulting in oliguric acute kidney injury. The known agents that cause osmotic nephropathy, include mannitol, contrast media and intravenous immunoglobulin. The similar lesion was first described in patients with poorly controlled diabetes or diabetic ketoacidosis in the late 1800s. However, it has been rarely seen for nearly a century, after the advent of insulin therapy and subsequent glucose lowering agents. Although it is premature to conclude that SGLT2 inhibitors caused osmotic nephropathy because of underlying diabetes and being based on a single case, and therefore needs further evaluation, this lesion could be associated with SGLT2 inhibitors, since these agents particularly increase the amount of urinary glucose, even on the condition of euglycemia, resulting in severe hyperglycosuria, that imposes a similar situation with the morphogenesis of osmotic nephropathy.

(Images and text were provided by Masayuki Yamanouchi, MD, MPH, Shun Watanabe, MD, Junichi Hoshino, MD, Yoshifumi Ubara, MD, Toranomon Hospital, Tokyo, Japan: Yutaka Yamaguchi, MD, Department of Pathology, Teikyo University School of Medicine, Tokyo, Japan: and Kenichi Ohashi, MD, Department of Pathology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan)