Case Report

Clinical response to sodium glucose co-transporter 2 inhibitor ipragliflozin in a patient with metastatic renal cell carcinoma

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Abbreviations & Acronyms
ccRCC = clear cell renal cell carcinoma
CT = computed tomography
mRCC = metastatic renal cell carcinoma
SGLT2 = sodium glucose co-transporter 2

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Introduction: Sodium glucose co-transporter 2 inhibitors constitute a new class of antidiabetic medication. Sodium glucose co-transporter 2 inhibitors have been shown to exert anticancer effects. However, the clinical value of these drugs as anticancer agents is yet to be evaluated.

Case presentation: A 72-year-old man presented to our hospital with frequent cough and dyspnea. Contrast-enhanced computed tomography revealed renal cell carcinoma cT3bN0M1. Ipragliflozin, a sodium glucose co-transporter 2 inhibitor, treatment was initiated to control blood glucose levels. Two years after diagnosis, computed tomography revealed remarkable tumor regression without any systemic therapy other than ipragliflozin.

Conclusion: Sodium glucose co-transporter 2 inhibitors are potentially applicable as anticancer agents among patients with metastatic renal cell carcinoma.

Key words: diabetes mellitus, renal cell carcinoma, sodium glucose transporter 2 inhibitor.

Keynote message

SGLT2 inhibitors have potential anticancer effects on mRCC. Epidemiological surveys are required to further elucidate the effects of SGLT2 inhibitors on renal cell carcinoma.

Introduction

mRCC treatment generally involves multimodal therapy including cytoreductive nephrectomy and systemic therapy including molecular-targeted drugs and immunotherapeutic agents.[1] However, the mortality rates of individuals with advanced mRCC remain high even after multimodal treatment.

SGLT2 inhibitors are a new class of therapeutic agents indicating type 2 diabetes mellitus, reducing glucose reabsorption in the renal proximal tubule, and plasma glucose levels.[2] A recent study reported that SGLT2 inhibitors have anticancer effects and reduce tumor growth in renal cell carcinoma *in vitro* and *in vivo*.[3] However, it has been unclear whether SGLT2 inhibitors clinically exert anticancer effects in mRCC.

Case presentation

A 72-year-old man presented at our hospital with frequent cough and dyspnea. He had history of diabetes mellitus and myocardial infarction. Chest CT revealed bilateral multiple lung nodules. Abdominal contrast-enhanced CT revealed an 86-mm left renal tumor, indicating ccRCC, a tumor thrombus in the left renal vein progressing to the inferior vena cava, and multiple liver metastases (Fig. 1). Memorial Sloan Kettering Cancer Center and International mRCC database consortium prognostic scores indicated intermediate and poor risk, respectively. The Karnofsky performance status score was 70, the neutrocyte count was 9800/μL, and hemoglobin level was 10.5 g/dL. Diagnosis revealed the cT3bN0M1 stage (liver and lung metastases) of metastatic ccRCC. However, the patient opted for palliative care without any

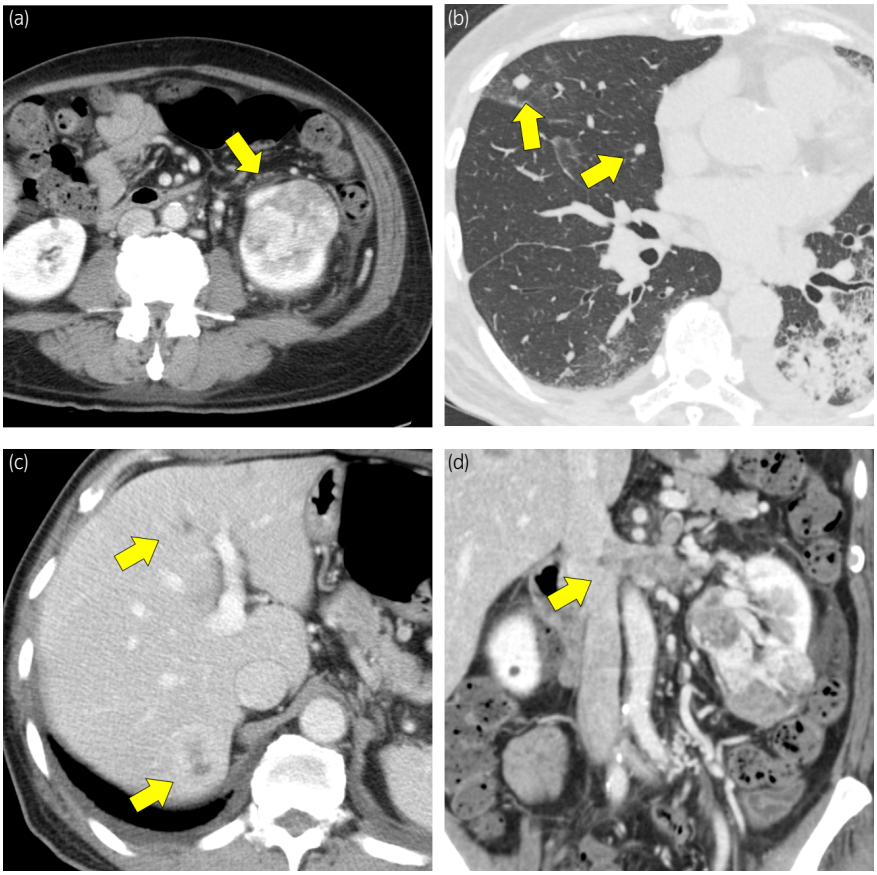

Fig. 1 Enhanced CT showing (a) the renal tumor, (b) multiple lung metastases, (c) liver metastases, and (d) tumor thrombus.

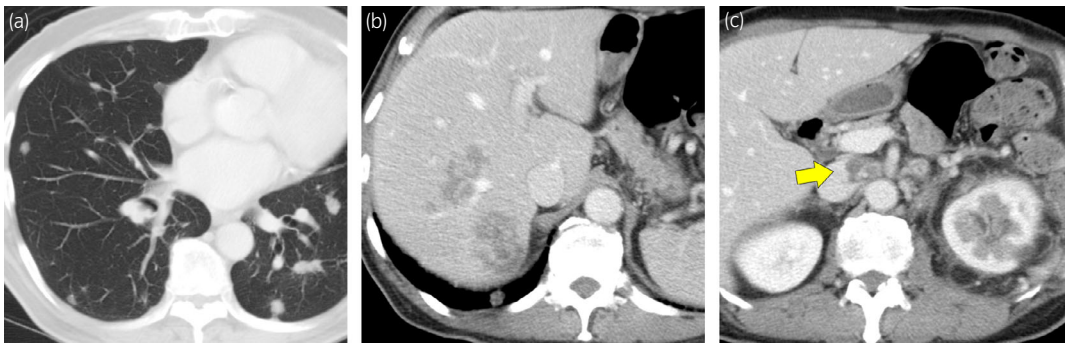

Fig. 2 Progression of (a) multiple lung metastases, (b) liver metastases, and (c) tumor thrombus.

further invasive investigation including biopsy. He experienced pedal edema and abdominal distention during the observation period. Blood glucose levels were gradually increased.

At 10 months after diagnosis, ipragliflozin 50 mg per day was initiated at a nearby clinic to control blood glucose levels. CT revealed progression of multiple lung metastases, liver metastases, and a tumor thrombus (Fig. 2). Consequently, pedal edema and abdominal distention improved, and blood glucose levels decreased. Two years after diagnosis, CT revealed regression of liver and lung metastases and tumor thrombus in the left renal vein (Fig. 3).

Discussion

Renal cell carcinoma accounts for 2–3% of all human malignancies. mRCC is predicted to either be present or later develop in approximately 30–40% of renal cell carcinoma patients.[1] Most mRCC patients have large, locally advanced tumors often with in regional nodes, the renal vein, and/or the inferior vena cava. mRCC patients are usually treated with multimodal therapy including cytoreductive nephrectomy, tyrosine kinase inhibitors, and immunotherapy.[1] However, the mortality rate of patients with advanced-stage mRCC is still high even after multimodal therapy.

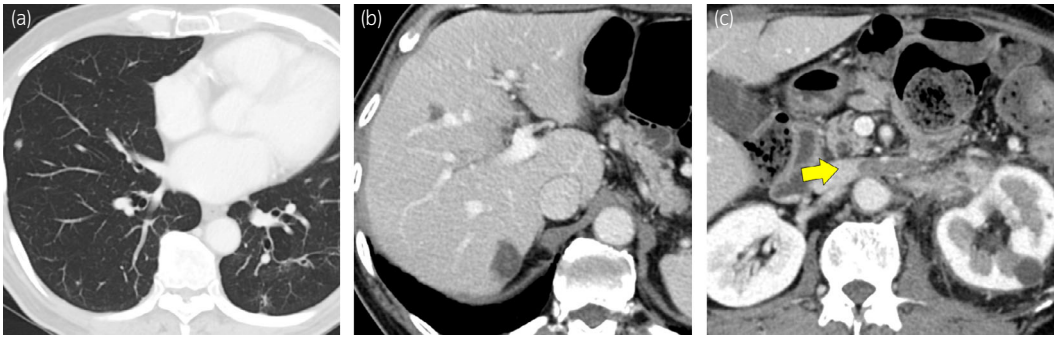

Fig. 3 Regression of (a) multiple lung metastases, (b) liver metastases, and (c) tumor thrombus 1 year after initiation of treatment with SGLT2 inhibitor.

In tumor cells, mitochondrial functions are suppressed, and energy is generated via glycolysis under aerobic and anaerobic conditions. Tumor cells adapt to aerobic glycolysis by increasing glucose uptake systems and altering the expression of metabolic enzymes.[2] Glucose uptake systems and metabolic enzymes are potential targets for anticancer therapies.

SGLT2 is a sodium glucose co-transporter expressed primarily in the renal cortex.[4] More than 90% of glucose filtered in the glomerulus is reabsorbed in the proximal tubules via SGLT2-mediated glucose uptake. Blockade of SGLT2 inhibits renal glucose reabsorption, thereby potentially decreasing blood glucose levels in individuals with diabetes mellitus. SGLT2 is reportedly expressed in various tumors, including renal cell carcinomas.[2] A recent study reported that dapagliflozin, an SGLT2 inhibitor, reduces the viability of renal cell carcinoma cell lines, thus regulating the cell cycle and apoptosis *in vitro* and *in vivo*.[3] In liver cancer cells, canaglifrozin inhibits cell growth by not only inhibiting glucose uptake but also by affecting intratumor angiogenesis.[5] It is possible that ipragliflozin affects both glucose uptake and tumor angiogenesis.

In the present case, the patient had advanced-stage mRCC without any systemic therapies. However, tumors regressed after initiation of ipragliflozin treatment. This is the first report of the clinical effect of SGLT2 inhibitor on mRCC. There are some limitations associated with this report. First, there is no histological confirmation of the renal tumor. Second, other than CT, no image analysis was performed. Therefore, we are unaware if any type of renal cell carcinoma regressed upon using ipragliflozin and the viability of this tumor. Ipragliflozin is a potential anticancer agent for renal cell carcinoma patients. SGLT2 inhibitors are already used widely in clinical practice, without serious side effects. Nonetheless, epidemiological surveys are required to further assess the effects of ipragliflozin on renal cell carcinoma.

Conflict of interest

The authors declare no conflict of interest.

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