

## Tumor lysis syndrome following sorafenib treatment in hepatocellular carcinoma

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Sorafenib is indicated for the treatment of advanced hepatocellular carcinoma (HCC), but although rare, tumor lysis syndrome (TLS) can be fatal in HCC patients with a large tumor burden. The authors describe the case of a 55-year-old hepatitis B carrier who visited our clinic with progressive dyspnea for 3 weeks. Chest and abdominal computed tomography revealed a huge HCC in the left lobe of the liver with invasion of the inferior vena cava, right atrium, and pulmonary arteries. After 8 days of sorafenib administration, TLS was diagnosed based on the characteristic findings of hyperuricemia, hyperkalemia, and acute kidney injury with massive tumor necrosis by follow-up imaging. Despite discontinuation of sorafenib and supportive care, the patient's clinical course rapidly deteriorated. The authors describe a rare but fatal complication that occurred soon after sorafenib initiation for HCC. Careful follow-up is required after commencing sorafenib therapy for the early diagnosis and management of TLS.

**Keywords:** Hepatocellular carcinoma; Sorafenib; Tumor lysis syndrome

### INTRODUCTION

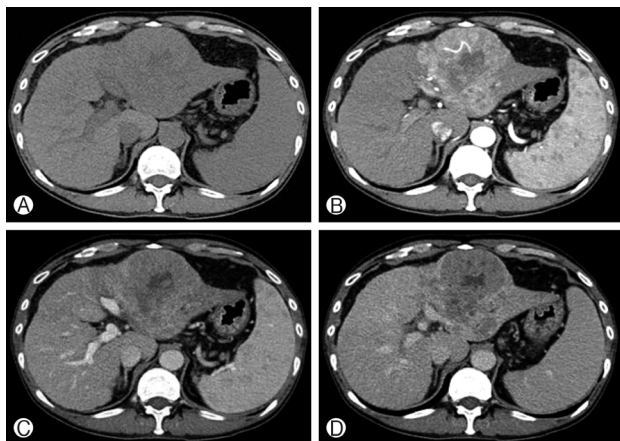
Tumor lysis syndrome (TLS) is a commonly encountered emergency in patients with a hematologic cancer, but is rare in patients with a solid tumor [1]. This syndrome is caused by release of the contents of malignant cells to blood, either spontaneously or in response to effective therapy [2]. Sorafenib, an oral multi-kinase inhibitor, blocks angiogenesis and tumor cell growth and provides proven survival benefits in advanced unresectable hepatocellular carcinoma (HCC) [3]. TLS has been reported in several cases of HCC after transarterial chemoembolization or radiofrequency ablation [4,5], but few reports of TLS following sorafenib treatment for HCC have been issued [6-8]. Here, we report a case of TLS that occurred 8 days after the administration of sorafenib in a patient with advanced HCC.

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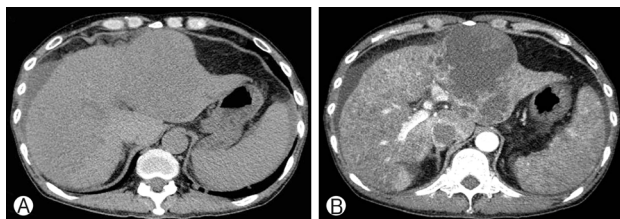
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### CASE

A 55-year-old male visited our clinic complaining of shortness of breath that had persisted for 3 weeks. Thirty years previously he had been diagnosed with hepatitis B, but had not been followed regularly. Chest X-ray showed multiple small nodular opacities in both lung fields, and chest computed tomography (CT) displayed numerous small nodules, suggesting hematogenous metastasis, pulmonary tumor embolism involving the right main pulmonary, right upper lobar, and both lower lobar pulmonary arteries, and tumor thrombosis invasion of the left hepatic vein, inferior vena cava, and right atrium. Dynamic liver CT revealed a 7.5-cm sized hypervascular mass with washout occupying the left lobe (Fig. 1). We diagnosed HCC invading vessels with multiple lung metastases. Laboratory data were as follows; hepatitis B e antigen (HBeAg) negative, hepatitis B e antibody (HBeAb) positive, hepatitis B virus DNA (LG Life Sciences, Korea) 21,129 copies/mL, white blood cell count 4,480/mm<sup>3</sup>, hemoglobin 13.6 g/dL, platelet count 96,000/mm<sup>3</sup>, aspartate aminotransferase (AST) 96 U/L (reference range, 0-40 U/L), alanine aminotransferase (ALT) 42 U/L (reference range, 0-46 U/L), lactate dehydro-



**Fig. 1.** Liver dynamic computed tomography images before treatment with sorafenib showing a 7.5-cm hypervascular mass with delayed washout in the left lobe. (A) Pre-enhanced phase, (B) arterial phase, (C) portal phase, and (D) delayed phase.



**Fig. 2.** Chest computed tomography images taken 8 days after sorafenib commencement showed a large region of tumor necrosis and thrombus within the intrahepatic inferior vena cava. (A) Pre-enhanced phase, (B) post-enhanced phase.

genase (LDH) 1,308 U/L (reference range, 218-472 U/L), total bilirubin (TB) 1.38 mg/dL (reference range, 0.2-1.2 mg/dL), albumin 4 g/L (reference range, 3.8-5.3 g/L), prothrombin time 13.6 s (control 10.9 s), creatinine 0.96 mg/dL (reference range, 0.5-1.3 mg/dL), uric acid 5.4 mg/dL (reference range, 2.8-8.3 mg/dL), sodium 135 mEq/L (reference range, 135-150 mEq/L), potassium 4.1 mEq/L (reference range, 3.5-5.1 mEq/L), calcium 8.6 mg/dL (reference range, 8.2-10.2 mg/dL), phosphorus 2.0 mg/dL (reference range, 2.5-4.5 mg/dL),  $\alpha$ -fetoprotein 1,795  $\mu$ g/L (reference range, 0-20  $\mu$ g/L), and prothrombin induced by vitamin K absence (PIVKA) II 19,717 mAU/mL. The patient was given oral sorafenib 400 mg b.i.d. and oral tenofovir 300 mg once daily, and was discharged 4 days after introducing sorafenib without adverse effect.

Eight days after sorafenib commencement, the patient complained of progressive dyspnea and generalized weakness. Chest CT showed progression of the pulmonary thromboembolism and tumor thrombosis in the right atrium. In addition,

a large region of necrosis was observed in the location of the previously enhancing mass in the left liver (Fig. 2). Laboratory data revealed an AST level of 5,729 U/L, ALT 2,370 U/L, LDH 17,971 U/L, TB 4.1 mg/dL, creatinine 0.85 mg/dL, uric acid 9.5 mg/dL, and potassium 5.3 mEq/L. Sorafenib was discontinued due to concerns of TLS development. However, on the following day, creatinine, uric acid, and potassium levels rose to 1.45 mg/dL, 11.5 mg/dL, and 5.8 mEq/L, respectively. The patient was diagnosed with TLS, and intravenous fluid replacement, diuretics, oral kalimate, bicarbonate, and allopurinol were administered. Although elevated AST and LDH levels began to decrease 2 days after discontinuing sorafenib, creatinine increased to 2.55 mg/dL and urine output decreased. Emergent hemodialysis was considered, but the family decided on transfer to a nursing home.

## DISCUSSION

TLS is a potentially life-threatening oncological emergency that is caused by the rapid breakdown of malignant cells and the release of their intracellular contents to blood [2]. The diagnosis of laboratory TLS is based on the presence of two or more of the following laboratory abnormalities: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Laboratory TLS accompanied by an elevated creatinine level, cardiac dysrhythmia, seizure, or death satisfies the criteria for clinical TLS [9]. Our patient presented with hyperuricemia, hyperkalemia, and an elevated creatinine level, and thus, met the diagnostic criteria for clinical TLS.

TLS typically develops in cases of hematological malignancy within a week after initiating an effective chemotherapy. On the other hand, TLS in HCC is expected to develop later and less frequently, because solid tumors grow at lower rates than hematologic malignancies and are more resistant to cytotoxic therapies [2]. However, the introduction of multi-targeted kinase inhibitors increased the risk of the early development of TLS in patients with solid tumors [10]. To date, the shortest time reported to the development of TLS after sorafenib commencement in a patient with HCC was 10 days [8], and in the present case, TLS and massive tumor necrosis developed only 8 days after starting sorafenib. TLS is more likely to develop in patients with hematological malignancies, highly proliferative tumors, a heavy tumor burden, or pre-existing renal impairment or after the initiation of a highly effective

treatment [2]. In our patient, the presence of a rapid growing large HCC nodule and the therapeutic efficacy of sorafenib may have led to massive tumor necrosis and early TLS development.

Sorafenib is administered orally, and can be prescribed in an outpatient department. Subsequently, patients are monitored for common adverse events, such as, hand-foot skin reactions, constitutional symptoms, and diarrhea [3]. However, although TLS following treatment with sorafenib is rare, it can be fatal as demonstrated by the present case. Patients with the manifestations of TLS should receive supportive care, including intravenous hydration, control of electrolyte disturbances, urine alkalinization, and hemodialysis when needed, in order to minimize oliguria and acidosis [2]. In the presented case, sorafenib was terminated after 8 days of treatment, but clinical TLS progressed despite supportive care. Recently, a case of grade I TLS and of impending TLS were reported in whom early suspicion and prompt management prevented further progression [7,8]. To avoid potentially fatal complications after sorafenib commencement, careful follow up for TLS is required in HCC patients with a large tumor burden or an aggressive tumor type.

In conclusion, clinicians should remember that although rare, TLS can occur soon after instituting sorafenib in cases of HCC with a large tumor burden. Close monitoring for the development of TLS is needed after starting sorafenib in advanced HCC with a heavy tumor burden. Furthermore, a high index of suspicion for TLS, immediate discontinuation of the drug, and supportive management can improve prognosis.

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