CASE REPORT

A case of paraneoplastic liver dysfunction with elevated serum interleukin-6 in clinically localized renal cell carcinoma

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Abstract We report a case of paraneoplastic liver dysfunction associated with a renal cell carcinoma, which disappeared after surgery. A 62-year-old male presented with fatigue and weight loss. The most prominent laboratory abnormality was elevated alkaline phosphatase, C-reactive protein, and interleukin-6 while normal aminotransferases. Computed tomography scan revealed a solid mass in the left kidney. A left radical nephrectomy was performed. After the surgery, biochemical abnormalities returned to normal.

Keywords Renal cell carcinoma · Paraneoplastic · Liver dysfunction · Interleukin-6

Introduction

Non-metastatic intrahepatic cholestasis and a reversal of these abnormalities after nephrectomy in patients with renal cell carcinoma (RCC) is a rare phenomenon known as Stauffer syndrome [1, 2]. Previous studies suggested an involvement of interleukin (IL)-6 in this paraneoplastic non-metastatic liver dysfunction [3]; however, IL-6 changes during perioperative periods have not been evaluated in patients with Stauffer's syndrome. We present a case of paraneoplastic liver dysfunction with elevated serum IL-6, which returned to normal following nephrectomy.

Case report

A 62-year-old male was admitted to our hospital because of fatigue, malaise and 6 kg body weight loss. He had a history of appendicitis treated with surgery. He had no family history of autoimmune disease or cancer. He denied any significant alcohol, tobacco, or drug abuse. On physical examination, the patient weighed 64 kg, was 163.8 cm tall, with body mass index of 23.9. He did not have jaundice or hepatosplenomegaly. There were no other significant physical findings. The most prominent laboratory abnormality was elevated serum liver enzymes which was consistent with cholestasis, including alkaline phosphatase (ALP) at 1961 IU/l (<320) and γ -glutamyl transferase at 223 IU/l (<90). ALP isoenzymes are ALP1 (liver) 41 %, ALP2 (liver) 57 %, ALP3 (bone) 2 % ALP4 (placenta) 0 %, ALP5 (intestine) 0 %, and ALP6 (immunoglobulin-bound) 0 %, respectively. Serum bilirubin and aminotransferases were normal. Hemoglobin was 9.8 g/dl, white cell 9300/ μ l, with a normal differential count, platelets 528,000/ mm^3 , C-reactive protein (CRP), 16.93 mg/dl (<0.35), and IL-6 134.0 pg/ml (<4). Serological tests for hepatitis B and C were negative, respectively. On ultrasound of the abdomen there was no evidence of liver mass. An abdominal computed tomography scan revealed a 7.0 cm $\times$ 7.0 cm $\times$ 6.0 cm, heterogeneously enhanced solid mass, which suggested clear cell RCC with sarcomatoid component, in the left kidney (Fig. 1). A left radical nephrectomy was performed. The histopathological examination revealed a clear cell renal carcinoma, a Fuhrman grade 3, invading the perirenal fat, and invading the left renal vein (pT3a). The surgical margins were free of tumor. The patient had an uneventful operative course and postoperative laboratory studies revealed normalization of his chemistries including ALP, CRP, and IL-6. Now the patient lives with no evidence of disease.

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Fig. 1 Contrast-enhanced CT images of abdomen. Transverse CT shows a 7.0 cm × 7.0 cm solid mass (white arrow) in left kidney

Discussion

RCC can present with a variety of paraneoplastic syndrome, such as increased erythrocyte sedimentation rate, anemia, cachexia, weight loss, fever, hypercalcemia, polycythemia, amyloidosis, neuromyopathy, and liver dysfunction [4]. Among those paraneoplastic findings, Stauffer's syndrome, a hepatic dysfunction without liver metastases, is a unique paraneoplastic manifestation of RCC. This syndrome often resolves with nephrectomy, and its return can indicate disease recurrence. Several basic and clinical studies indicate the importance of the proinflammatory cytokine IL-6 to this paraneoplastic hepatic dysfunction. In vitro studies, RCC cell lines have been shown to express IL-6 receptor and produce IL-6, suggesting IL-6 function as autocrine growth factor [5]. In addition, up to 50 % of patients with metastatic RCC have increased levels of circulating IL-6, correlate with increased CRP and ALP levels [3, 6]. Those findings from previous studies lead to the speculation that IL-6 produced from RCC cells, which works as an autocrine growth factor, has effect on liver cells and resulted in increase of CRP as well as ALP in this syndrome. Indeed, IL-6 cytokine family is known to induce expression of acute phase proteins, including CRP in hepatocytes [7]. In most situations, induction of the

acute phase proteins by IL-6 has been regarded as part of an attempt to control inflammation or tissue injury. In Stauffer's syndrome, tumor-derived IL-6 worked on hepatocytes resulting in acute phase reaction, in trying to maintain homeostasis. On the other hand, the relationship between IL-6 and ALP elevation, which mainly reflects cholangiocyte injury, still remains unclear. Increased liver ALP isoenzyme level may indicate that they are produced from bile duct epithelial cells. Our patient's liver dysfunction likely resulted from excess IL-6 production by the renal tumor and he demonstrated marked clinical improvement of all symptoms, including normalization of all laboratory values following nephrectomy. Although there are many reports about this syndrome, the case with clinically localized RCC with postoperative normalization of serum IL-6 is not found. We guess that our case adds to the growing pool of data of Stauffer's syndrome.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human subjects All procedures performed in this report involving human participants were in accordance with the ethical standards of the institutional ethical committee.

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