76840_Auto_Edited.docx

WORD COUNT 2646
TIME SUBMITTED 15-JUL-2022 04:14PM
PAPER ID 88434839

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 76840
Manuscript Type: CASE REPORT

Renal cell carcinoma presented with a rare case of icteric Stauffer syndrome: A case report

Popov DR *et al.* Rare icteric Stauffer syndrome

Dimitar R Popov, Krasimir A Antonov, Evelina G Atanasova, Christo P Pentchev, Lyuben M Milatchkov, Maria D Petkova, Krasimir G Neykov, Rosen K Nikolov

Abstract

BACKGROUND

Paraneoplastic syndromes remain poorly understood and manifest with multifaceted clinical symptoms, making their diagnosis difficult. Cholestasis can be observed in various malignancies. In rare cases, it can be a paraneoplastic manifestation most often associated with renal cell carcinoma and other urogenital tumors, as well as with bronchial carcinoma. The classical form of Stauffer syndrome is presented with a reversible anicteric increase of cholestatic liver function tests, thrombocytosis, coagulation impairment and hepatosplenomegaly, without any proven hepatobiliary obstruction or metastases.

CASE SUMMARY

We report a patient who presented with elevated liver enzymes, cholestatic jaundice, weight loss and pruritus, in whom renal cell carcinoma was incidentally found during hospitalization. Clinical, laboratory and imaging tests excluded primary hepatic cause or metastatic disease. The jaundice and the laboratory abnormalities reverted completely a few months after nephrectomy. This case is an example for the many faces of renal cell

carcinoma, and it raises the attention of the clinicians when suspecting Stauffer syndrome and its variant in the differential diagnosis of cholestasis. Thus, the correct diagnosis can be set quickly and the associated malignancy can be treated promptly. All cases should be followed-up by a multidisciplinary team. Interleukin (IL)-6 is assumed to contribute to the pathophysiology of the condition. The proposed mechanism is proinflammatory activity by the IL-6 cytokine causing elevation of C-reactive protein and haptoglobin and inhibition of hepatobiliary transporter gene expression, impairing biliary outflow.

CONCLUSION

Despite being rare, Stauffer syndrome is a potentially reversible paraneoplastic condition, when the primary cause is treatable. This syndrome should be considered by clinicians because of the remediable liver disturbance, after successful treatment of the underlying malignancy.

Key Words: Case report; Jaundice; Cholestasis; Renal cell carcinoma; Stauffer syndrome

Popov DR, Antonov KA, Atanasova EG, Pentchev CP, Milatchkov LM, Petkova MD, Neykov KG, Nikolov RK. Renal cell carcinoma presented with a rare case of icteric Stauffer syndrome: A case report. *World J Clin Cases* 2022;

Core Tip: Initial presentation of jaundice, in cases of non-hepatic malignancy, is generally associated with metastatic liver disease. Despite the increased bilirubin levels, surgical treatment, when possible, is an appropriate approach in a case with non-metastatic cholestatic syndrome. Stauffer syndrome is a rare presentation of kidney and urinary tract malignancies and even rarer when presented with jaundice.

INTRODUCTION

In 1961, Herbert Maurice Stauffer, an American gastroenterologist, first described a syndrome associated with hypernephroma, low blood levels of albumin, elevated gamma

globulins, high alkaline phosphatase (AP) and prolonged prothrombin time, with normalization of liver function tests achieved upon successful treatment of the underlying malignancy[1]. Stauffer syndrome is observed in 3% to 6% of cases of renal cell carcinoma (RCC)[2]. Lymphocytic infiltration and cellular degeneration of the liver clinically present elevated hepatic enzymes and impaired liver function in the absence of liver metastases[3]. At least two theories about the pathogenesis are hypothesized, and include: (1) Liver damage due to stimulation of cathepsins and hepatic phosphatases by hepatotoxins or lysosomal enzymes; and (2) Direct liver damage and the subsequent immune response[4]. Among the substances produced are granulocyte-macrophage colony stimulating factor and interleukin (IL)-6 are notable. Other admissible speculations include generalized hepatic hypervascularity, amyloid deposition, and autoimmune phenomenon[5]. This case is reported in line with the criteria of the 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE)[6].

CASE PRESENTATION

Chief complaints

A 68-year-old Caucasian male was admitted to our clinic to address ongoing intensive jaundice, fatigue, pruritus, pain and heaviness in the right upper quadrant of the abdomen that had persisted since September 2020.

History of present illness

The patient had been admitted to another medical center, and acute and chronic viral hepatitis were excluded by the following negative markers: hepatitis B surface antigen; anti-hepatitis B core immunoglobulin M (IgM); anti-hepatitis C virus; anti-hepatitis A virus IgM; cytomegalovirus IgM; hepatitis B virus DNA; and hepatitis C virus RNA. Autoimmune and metabolic liver diseases were excluded as well by negative serologic marker testing for autoimmune hepatitis, and by levels of IgG and IgM within the reference range. Slightly increased ceruloplasmin was observed. Ultrasound examination revealed tumor (45 mm × 32 mm) formation in the right kidney. Native magnetic

resonance imaging (MRI)-cholangiopancreatography (MRCP) was performed, which was negative for biliary pathology and confirmed tumor formation with expansive growth and compression of the lower surface of the right liver lobe. For clarification, liver biopsy was performed and showed a histological view most compatible with toxic hepatitis, with no stigma for primary biliary cholangitis, hepatitis or cirrhosis. Treatment consisting of ademetionine, silymarin, L-ornithine, L-aspartate, methylprednisolone 60 mg per day intravenous (i.v.) for 8 d, ursodeoxycholic acid 1000 mg per day, vitamin K i.v., antibiotics, and antisecretory and i.v. fluids was administered but produced no obvious effect.

History of past illness

The patient had a history of arterial hypertension, ischemic stroke (in 2007), and vertigo (as a result of the latter). A perianal fistula had been present in adolescence.

Personal and family history

Neither family history nor allergies were reported by the patient.

Physical examination

On October 2, 2020, the patient was admitted with the above-mentioned complaints for the first time to our Gastroenterology clinic. Physical examination showed jaundice of the skin and sclera, skin excoriations, hepatomegaly, and slight abdominal tenderness.

Laboratory examination

The preoperative laboratory findings are displayed in Table 1. After reconfirmation of negative virological tests, including anti-hepatitis E virus (HEV) IgM (-), Epstein-Barr virus IgM (-) and anti-HEV IgG (+), a positive result was established. However HEV RNA was undetectable. The levels of lactate dehydrogenase, ceruloplasmin, IgA, IgG and IgM were normal. Chronic poisoning by lead, manganese and arsenic was rejected. Tuberculosis was excluded by QuantiFERON-TB Gold Plus assay (Qiagen, Hilden,

Germany). Levels of fetal oncoproteins, total prostate-specific antigen, alpha-fetoprotein and CA 19-9 were within normal ranges.

Additionally, dyslipidemia was detected, with total cholesterol at 18.1 mmol/L (reference range: < 5.2 mmol/L), low-density lipoprotein at 16.0 mmol/L (< 3.0), triglycerides at 3.3 mmol/L (< 2.0), and high-density lipoprotein at 0.6 mmol/L (> 0.9 mmol/L). During follow-up after the nephrectomy, lipid panel levels reached normal rates, including that of cholesterol (3.9 mmol/L), low-density lipoprotein (1.7 mmol/L), triglycerides (0.6 mmol/L), and high-density lipoprotein (1.3 mmol/L).

Imaging examinations

Abdominal ultrasound showed the liver and spleen to be of normal dimensions. No features of biliary or pancreatic morphology changes or portal hypertension were detected. A heterogeneous, rounded lesion (45 mm × 32 mm) was visualized at the upper pole of the right kidney, with detectable arterial signal on Doppler examination (Figure 1A and B).

Further, contrast-enhanced computed tomography (CT) of the abdomen was performed. The liver was shown to have slightly lobulated contour, hypertrophy of segment I and normal parenchymal density, without pathological lesions or post-contrast enhancement, and non-dilated intra- and extrahepatic bile ducts. The tumor (46 mm × 31 mm) formation in the right kidney was confirmed and found to have invaded the vena cava inferior. The tumor reached the liver parenchyma at segment VI, without infiltration (Figure 1C).

Chest X-ray examination revealed no infiltrative or focal lesions.

FURTHER DIAGNOSTIC WORK-UP

Findings from the liver biopsy specimens and MRI of the abdomen from the first medical center were reviewed, but provided no other explanation of the observed changes in the liver function tests.

FINAL DIAGNOSIS

After clinical discussion (with careful consideration of all clinical findings, including results from the laboratory tests and imaging studies, and reference to similar cases in the literature), the patient was diagnosed with a paraneoplastic syndrome in urogenital tumors and Stauffer syndrome.

TREATMENT

Therapy consisted of ademetionine (administered September 4, 2020 to December 17, 2020), N-acetyl cysteine (October 2, 2020 to present), thiamine and pyridoxine, methylprednisolone (20 mg/d i.v. for 8 d), broad-spectrum antibiotics, gastro protectors, and i.v. fluids, including colloid solutions (*i.e.* human albumin); unfortunately, no improvement was achieved (according to unchanged laboratory test findings). Instead, the patient experienced a progressive increase in total and direct bilirubin as well as an increase in gamma-glutamyl transferase and AP levels.

As the syndrome is characterized by non-metastatic liver damage caused by hormones and substances secreted by the tumor (including IL-6), we determined that the patient was suitable for surgical treatment. The case was presented to the oncologist, and all of the risks and benefits of potential surgical intervention were carefully assessed. The patient was then referred for nephrectomy in our oncology clinic at The National Oncology Centre.

In the preoperative workup, IL-6 was 24.12 ng/mL (normal level: < 7.00). On October 16, 2020, an open right nephroureterectomy was performed. On the third postoperative day, the patient developed bleeding from the drainage, which required a revision surgery and hemostasis of small venous vessels that had grown to the liver. Histology indicated a clear cell, G2 type RCC, with a diameter of 3 cm and tumor thrombus in the lumen of the vena cava inferior, staged as pT3bNxMx G2 LVI (Figure 2).

The peri- and postoperative laboratory findings are summarized in Table 2 and expressed graphically in Figure 3.

The Oncology Committee recommended adjuvant radiotherapy to be initiated when findings of liver function tests reached normal range.

OUTCOME AND FOLLOW-UP

The patient was followed-up until November 30, 2020, when he was re-admitted to our Gastroenterology Clinic due to persistence of the jaundice and intensive pruritus despite ongoing treatment with hepatoprotectors, antiacids, and antihypertensive therapy. On routine abdominal ultrasound study, the imaging showed no dynamics of the liver or portal blood flow. An additional finding worth mentioning was a mild decrease in cholinesterase and a drop in IL-6 level. Supportive therapy was continued, and antifungal and anaerobe prophylactics were added.

The patient was discharged when slight clinical and laboratory improvement was achieved, and outpatient hepatoprotective and antioxidant therapies were ordered. On January 20, 2021, restaging was conducted *via* positron emission tomography (PET)-CT and provided no convincing data of residual tumor tissue, locoregional relapse, or distant dissemination related to the oncological process.

The current performance status of the patient is 1 and PET-CT monitoring has shown no indications of local relapse or distant dissemination.

DISCUSSION

RCC is related to various paraneoplastic syndromes classified as endocrine and non-endocrine[7]. RCC represents 2% to 4% of all newly diagnosed cancers announced in the developed countries annually, making it the most common primary renal malignant tumor[8]. According to data from the American Cancer Society in 2015, the 5-year survival rates for localized tumor are satisfactory; yet, metastases are not exceptional in the course of disease. Practically, 20% of the patients demonstrate metastases at the initial diagnostic work up. 20% to 40% of all patients who undergo curative nephrectomy, will develop RCC metastases[9,10]. The most common metastatic site is the liver, which induces a significant decrease in the 5-year survival rate (to 20%)[11].

Nowadays, when we already know considerably a lot about carcinogenesis and the pathways of metastasis of most of the malignant diseases, paraneoplastic syndromes remain poorly understood and manifest with multifaceted clinical symptoms, making their diagnosis difficult. Cholestasis can be observed in various malignancies-liver, pancreas, gall bladder and bile ducts. It can be due to obstruction of the biliary tree or liver metastases. In rare cases, cholestasis is a paraneoplastic manifestation-Stauffer syndrome; classically seen in RCC, it has also been described in prostate, bronchial, and urinary bladder malignancies. It is mainly presented with cholestatic liver function tests increase, thrombocytosis and coagulation impairment without any proven liver metastases.

The most common laboratory findings are elevated AP (90% of cases), hyperbilirubinemia (15%), and elevated transaminases (21%)[12].

The process is probably caused by IL-6, a proinflammatory cytokine secreted by cancer cells, since impaired laboratory results normalize after anti-IL-6 monoclonal antibody therapy. Clinical symptoms and laboratory disorders often persist during active malignancy but return to normal postoperatively[13].

The reported frequencies of Stauffer syndrome range between 3% and 20% of RCC cases[7]. Elevated IL-6 is often present, and associations between the levels of IL-6, AP, C-reactive protein (CRP) and haptoglobin have been reported in the event of RCC[14,15].

IL-6, in particular, has been proposed to play a major role in the pathophysiology of this syndrome[2,12,16]. Bhangoo *et al*[15] proposed a mechanism in which the proinflammatory activity of IL-6 causes impairment of biliary outflow *via* elevation of CRP and haptoglobin, and inhibition of the hepatobiliary transporter gene expression.

Recently, a more uncommon variant of the syndrome that initially presents with jaundice (icteric cholestasis) was described. According to Chavarriaga *et al*[17], there have been 11 cases of paraneoplastic cholestatic jaundice syndrome, including their case, reported in the literature.

In 1997, Dourakis *et al*[2] first reported 2 cases of this rare variant, which were presented with jaundice, pruritus and darker urine. The first case described a 65-year-old

woman with no history of hepatobiliary disease, which had a 25-mm renal tumor, detected incidentally by abdominal CT scan. After right nephrectomy was performed, a clear cell RCC was confirmed histologically. All abnormalities in her clinical condition and liver tests returned to normal after the operation. The second case described a 48-year-old male with a space-occupying lesion of the right kidney, discovered by a CT scan of his abdomen. A successful right nephrectomy was performed, with complete normalization of the clinical and laboratory findings after surgery.

In 2005, Giannakos *et al*[18] described a case of a 73-year-old male who complained of pruritus, painless jaundice, hyperpigmented urine and enlarged liver was found during the physical examination. A 30-mm tumor was described in the right kidney, and the patient underwent curative nephrectomy. The diagnosis of clear cell RCC was proven histologically, and all of the clinical and laboratory findings completely normalized after the surgery. None of the above cases had evidence of metastatic disease.

According to a recent review from Elseidy *et al*[19] (from 2022), diagnostic criteria for Stauffer syndrome are currently lacking. A stepwise diagnostic plan was proposed that includes liver function tests, abdominal ultrasound, MRCP and contrast-enhanced CT of the abdomen and pelvis. Multidisciplinary team meeting is recommended by the authors to take place before treatment initiation. This diagnostic plan is similar to the one that was applied by our team for the case described herein.

It is known that patients with obstructive jaundice have increased operative mortality rates, increased risk of infections, disseminated intravascular coagulation, gastrointestinal bleeding, delayed wound healing, wound dehiscence, *etc*[20]. This case report clearly demonstrates successful operative treatment despite higher perioperative risk. The strength of this study is in the multidisciplinary approach to making the decision for surgery of the patient with established liver failure. A limitation of the study is the lack of the baseline examination of IL-6 levels, as one of the explanations of dynamic changes in IL-6 values may be the invasive procedure itself. Another limitation is the fact that there was a positive result for anti-HEV IgG without any data for a past viral

infection. However, during the hospital stay, active infection from HEV was excluded. In cases of absent diagnostic criteria, the case is solved as a diagnosis of exclusion.

CONCLUSION

Stauffer syndrome and the icteric form (the rarest variant) should be considered as a possibility of an underlying neoplastic process in cases of unexplained liver impairment. Reversibility of the liver damage after successful treatment of the underlying malignancy should not be underestimated. The opinion of our team is that in order to quickly reach a diagnosis, clinicians of various related specific fields should be aware of the condition. Despite the rarity of the syndrome, further investigation for improvement of the diagnosis and treatment should be initialized.

ACKNOWLEDGEMENT

The authors are thankful to the Department of Urology, University Hospital of Oncology, Sofia, Bulgaria for performing the surgical treatment and post-surgical care of this patient, and to Prof. Radina Ivanova for the histology image.

76840_Auto_Edited.docx

ORIGINALITY REPORT

2%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.wjgnet.com Internet	22 words — 1%
2	www.ncbi.nlm.nih.gov Internet	14 words — 1%
3	www.tandfonline.com Internet	13 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS