MINIREVIEWS

8808  Ear, nose, and throat manifestations of COVID-19 and its vaccines
      Al-Ani RM

8816  Potential influences of religiosity and religious coping strategies on people with diabetes
      Onyishi CN, Eseadi C, Ilechukwu LC, Okoro KN, Okolie CN, Egbule E, Asogwa E

ORIGINAL ARTICLE

Case Control Study

8827  Effectiveness of six-step complex decongestive therapy for treating upper limb lymphedema after breast cancer surgery

Retrospective Study

8837  Hospital admissions from alcohol-related acute pancreatitis during the COVID-19 pandemic: A single-centre study
      Mak WK, Di Mauro D, Pearce E, Karran L, Myintmo A, Duckworth J, Orabi A, Lane R, Holloway S, Manzelli A, Mossadegh S

8844  Indocyanine green plasma clearance rate and 99mTc-galactosyl human serum albumin single-photon emission computed tomography evaluated preoperative remnant liver
      Iwaki K, Kathara S, Kita R, Kitamura K, Hashida H, Uryuhara K

8854  Arthroscopy with subscapularis upper one-third tenodesis for treatment of recurrent anterior shoulder instability independent of glenoid bone loss

8863  Evaluation of the prognostic nutritional index for the prognosis of Chinese patients with high/extremely high-risk prostate cancer after radical prostatectomy
      Yang F, Pan M, Nie J, Xiao F, Zhang Y

Observational Study

8872  Chlorine poisoning caused by improper mixing of household disinfectants during the COVID-19 pandemic: Case series
      Lin GD, Wu JY, Peng XB, Lu XX, Liu ZY, Pan ZG, Qiu ZW, Dong JG

8880  Mental health of the Slovak population during COVID-19 pandemic: A cross-sectional survey
      Kralova M, Brazinova A, Sivcova V, Izakova L
<table>
<thead>
<tr>
<th>Page No.</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>8893</td>
<td>Arthroscopic anatomical reconstruction of lateral collateral ligaments with ligament advanced reinforcement system artificial ligament for chronic ankle instability</td>
<td>Wang Y, Zhu JX</td>
</tr>
<tr>
<td>8906</td>
<td>How to select the quantitative magnetic resonance technique for subjects with fatty liver: A systematic review</td>
<td>Li YW, Jiao Y, Chen N, Gao Q, Chen YK, Zhang YF, Wen QP, Zhang ZM</td>
</tr>
<tr>
<td>8922</td>
<td>Lymphocytic choriomeningitis virus: An under-recognized congenital teratogen</td>
<td>Ferenc T, Vajic M, Mezljak A, Vilibic-Cavlek T</td>
</tr>
<tr>
<td>8939</td>
<td>Colo-colonic intussusception with post-polypectomy electrocoagulation syndrome: A case report</td>
<td>Moon JY, Lee MR, Yim SK, Ha GW</td>
</tr>
<tr>
<td>8945</td>
<td>Portal vein gas combined with pneumatosis intestinalis and emphysematous cystitis: A case report and literature review</td>
<td>Hu SF, Liu HB, Hao YY</td>
</tr>
<tr>
<td>8954</td>
<td>Quadricuspid aortic valve and right ventricular type of myocardial bridging in an asymptomatic middle-aged woman: A case report</td>
<td>Sopek Merkaš I, Lakušić N, Paar MH</td>
</tr>
<tr>
<td>8962</td>
<td>Treatment of gastric carcinoma with lymphoid stroma by immunotherapy: A case report</td>
<td>Cui YJ, Ren YY, Zhang HZ</td>
</tr>
<tr>
<td>8968</td>
<td>Gallstone associated celiac trunk thromboembolisms complicated with splenic infarction: A case report</td>
<td>Wu CY, Su CC, Huang HH, Wang YT, Wang CC</td>
</tr>
<tr>
<td>8974</td>
<td>Extracorporeal membrane oxygenation for lung cancer-related life-threatening hypoxia: A case report</td>
<td>Yoo SS, Lee SY, Choi SH</td>
</tr>
<tr>
<td>8980</td>
<td>Multi-disciplinary treatment of maxillofacial skeletal deformities by orthognathic surgery combined with periodontal phenotype modification: A case report</td>
<td>Liu JY, Li GF, Tang Y, Yan FH, Tan BC</td>
</tr>
<tr>
<td>8990</td>
<td>X-linked recessive Kallmann syndrome: A case report</td>
<td>Zhang P, Fu JY</td>
</tr>
<tr>
<td>8998</td>
<td>Delayed complications of intradural cement leakage after percutaneous vertebroplasty: A case report</td>
<td>Ma QH, Liu GP, Sun Q, Li JG</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>9012</td>
<td>Misdiagnosis of pancreatic metastasis from renal cell carcinoma: A case report</td>
<td>Liang XK, Li LJ, He YM, Xu ZF</td>
</tr>
<tr>
<td>9020</td>
<td>Discoid medial meniscus of both knees: A case report</td>
<td>Zheng ZR, Ma H, Yang F, Yuan L, Wang GD, Zhao XW, Ma LF</td>
</tr>
<tr>
<td>9028</td>
<td>Simultaneous laparoscopic and arthroscopic excision of a huge juxta-articular ganglionic cyst compressing the sciatic nerve: A case report</td>
<td>Choi WK, Oh JS, Yoon SJ</td>
</tr>
<tr>
<td>9036</td>
<td>One-stage revision arthroplasty in a patient with ochronotic arthropathy accompanied by joint infection: A case report</td>
<td>Wang XC, Zhang XM, Cai WL, Li Z, Ma C, Liu YH, He QL, Yan TS, Cao XW</td>
</tr>
<tr>
<td>9044</td>
<td>Bladder paraganglioma after kidney transplantation: A case report</td>
<td>Wang L, Zhang YN, Chen GY</td>
</tr>
<tr>
<td>9050</td>
<td>Total spinal anesthesia caused by lidocaine during unilateral percutaneous vertebroplasty performed under local anesthesia: A case report</td>
<td>Wang YF, Bian ZY, Li XX, Hu YX, Jiang L</td>
</tr>
<tr>
<td>9057</td>
<td>Ruptured splenic artery aneurysms in pregnancy and usefulness of endovascular treatment in selective patients: A case report and review of literature</td>
<td>Lee SH, Yang S, Park I, Im YC, Kim GY</td>
</tr>
<tr>
<td>9064</td>
<td>Gastrointestinal metastasis secondary to invasive lobular carcinoma of the breast: A case report</td>
<td>Li LX, Zhang D, Ma F</td>
</tr>
<tr>
<td>9071</td>
<td>Post-bulbar duodenal ulcer with anterior perforation with kissing ulcer and duodenocaval fistula: A case report and review of literature</td>
<td>Alzerwi N</td>
</tr>
<tr>
<td>9078</td>
<td>Modified orthodontic treatment of substitution of canines by first premolars: A case report</td>
<td>Li FF, Li M, Li M, Yang X</td>
</tr>
<tr>
<td>9087</td>
<td>Renal cell carcinoma presented with a rare case of icteric Stauffer syndrome: A case report</td>
<td>Popov DR, Antonov KA, Atanasova EG, Pentchev CP, Milatchkov LM, Petkova MD, Neykov KG, Nikolov RK</td>
</tr>
</tbody>
</table>
### Contents

**Thrice Monthly Volume 10 Number 25 September 6, 2022**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>9112</td>
<td>Congenital hepatic cyst: Eleven case reports</td>
<td>Du CX, Lu CG, Li W, Tang WB</td>
</tr>
<tr>
<td>9121</td>
<td>Endovascular treatment of a ruptured pseudoaneurysm of the internal carotid artery in a patient with nasopharyngeal cancer: A case report</td>
<td>Park JS, Jang HG</td>
</tr>
<tr>
<td>9127</td>
<td>Varicella-zoster virus meningitis after spinal anesthesia: A case report</td>
<td>Lee YW, Yoo B, Lim YH</td>
</tr>
<tr>
<td>9132</td>
<td>Chondrosarcoma of the toe: A case report and literature review</td>
<td>Zhou LB, Zhang HC, Dong ZG, Wang CC</td>
</tr>
<tr>
<td>9142</td>
<td>Tamsulosin-induced life-threatening hypotension in a patient with spinal cord injury: A case report</td>
<td>Lee JY, Lee HS, Park SB, Lee KH</td>
</tr>
<tr>
<td>9148</td>
<td>CCNO mutation as a cause of primary ciliary dyskinesia: A case report</td>
<td>Zhang YY, Lou Y, Yan H, Tang H</td>
</tr>
<tr>
<td>9156</td>
<td>Repeated bacteremia and hepatic cyst infection lasting 3 years following pancreatoduodenectomy: A case report</td>
<td>Zhang K, Zhang HL, Guo JQ, Tu CY, Lv XL, Zhu JD</td>
</tr>
<tr>
<td>9162</td>
<td>Idiopathic cholesterol crystal embolism with atheroembolic renal disease and blue toes syndrome: A case report</td>
<td>Cheng DJ, Li L, Zheng XY, Tang SF</td>
</tr>
<tr>
<td>9168</td>
<td>Systemic lupus erythematosus with visceral varicella: A case report</td>
<td>Zhao J, Tian M</td>
</tr>
</tbody>
</table>

**LETTER TO THE EDITOR**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>9176</td>
<td>Imaging of fibroadenoma: Be careful with imaging follow-up</td>
<td>Ece B, Aydin S</td>
</tr>
</tbody>
</table>
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Renal cell carcinoma presented with a rare case of icteric Stauffer syndrome: A case report

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

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Abstract

BACKGROUND
Paraneoplastic syndromes remain poorly understood and manifest as 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 presents 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. Jaundice and laboratory abnormalities reversed completely a few months after nephrectomy. This case is an example of the many sides of renal cell carcinoma, and it focuses the clinicians’ attention on the differential diagnosis of cholestasis, including Stauffer syndrome and its variant. Thus, the correct diagnosis can be straightforward and the associated malignancy can be treated promptly. All cases should be followed up with a multidisciplinary team. Interleukin (IL)-6 is proposed to contribute to the pathophysiology of the condition. The probable mechanism is proinflammatory activity by the IL-6 cytokine, causing elevation of C-reactive protein and
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: Jaundice; Cholestasis; Renal cell carcinoma; Stauffer syndrome; Case report

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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: liver damage due to stimulation of cathepsins and hepatic phosphatases by hepatotoxins or lysosomal enzymes; and 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**
The patient’s personal and family histories were unremarkable.

**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). Furthermore, contrast-enhanced computed tomography (CT) of the abdomen was performed. The liver had slightly lobulated contour, hypertrophy of segment I and normal parenchymal density, without pathological lesions or postcontrast enhancement, and non-dilated intrahepatic and extrahepatic bile ducts. 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 lesion.

**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 3rd 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 perioperative and postoperative laboratory findings are summarized in Table 2 and expressed graphically in Figure 3.
### Table 2 Perioperative and postoperative laboratory results

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>1.19</td>
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<td>Procalcitonin &lt; 0.046, in ng/mL</td>
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Alb: Albumin; ALT: Alanine aminotransferase; AP: Alkaline phosphatase; AST: Aspartate aminotransferase; Creat: Creatinine; Dbil: Direct bilirubin; GGT: Gamma-glutamyl transferase; IL-6: Interleukin-6; INR: International normalized ratio; Tbil: Total bilirubin.

### Figure 2

**Histology findings of the patient’s kidney tumor.** Clear cell renal cell carcinoma was observed, of Grade 2 (World Health Organization/International Society of Urological Pathology) and with focal areas of necrosis. Hematoxylin and eosin stain, 100 × magnification.

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, antacids, 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...
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 in the developed countries on an annual basis, making it the most commonly encountered primary renal malignant tumor[8]. According to data from the American Cancer Society in 2015, the 5-year survival rates for localized tumor are high. Controversially, metastases are commonly found. In fact, during the primary diagnostic work up, 20% of the patients present with metastatic spread. Eventually 20% to 40% of all patients will develop RCC metastases after radical nephrectomy[9,10]. The liver is amongst the most common metastatic site, leading to a significant decrease in the 5-year survival rate (to 20%)[11].

Despite the vast knowledge of carcinogenesis and metastasis spread of most of the malignant diseases, paraneoplastic syndromes remain poorly understood. Due to the multifaceted clinical presentation, their diagnosis remain difficult. Cholestasis can be observed in various malignancies such as the liver, pancreas, gall bladder, and bile ducts. It can be due to an 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 elevated cholestatic liver function tests, thrombocytosis, coagulation impairment and hepatosplenomegaly, in the absence of hepatic metastasis. 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 produced by cancer cells, since impaired laboratory results normalize after anti-IL-6 monoclonal antibody therapy. Clinical symptoms and laboratory abnormalities often persist during active malignancy but improve with nephrectomy [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] described 2 cases: of a 65-year-old woman and a 48-year-old male. They both were presented with jaundice and urinary hyperpigmentation and were diagnosed with renal carcinoma. After nephrectomy the conditions in both cases improved. These were the first described cases of icteric Stauffer syndrome.

In 2005, Giannakos et al[18] reported a similar case. A 73-year-old male presented with pruritus, painless jaundice, hyperpigmented urine and enlarged liver. The patient was diagnosed with clear cell RCC and underwent radical nephrectomy, after which normalization of abnormalities was observed. 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.

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.

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FOOTNOTES

Author contributions: Popov DR, Antonov KA, and Nikolov RK conceived and supervised the study; Atanasova EG, Pentchev CP, Milatchkov LM, and Petkova MD collected the clinical data and followed up with the patient; Popov DR and Antonov KA analyzed the data; Neykov KG contributed to the nephrectomy procedures; Pentchev CP, Atanasova EG, Milatchkov LM, and Petkova MD wrote the paper; all authors have read and approved the final manuscript.

Informed consent statement: The authors declare that the person involved in the case report gave his informed consent to be involved in the study. The informed consent has been provided to the publisher.

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