CASE REPORT

Stauffer's Syndrome Variant with Cholestatic Jaundice

A Case Report

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Cholestasis is a common feature of several malignant diseases, including pancreatic, hepatic, gallbladder, and ampullary carcinomas. It is usually secondary to main bile duct obstruction or widespread hepatic metastasis, but it can also be a paraneoplastic syndrome of other underlying malignancies. Stauffer's syndrome is a rare paraneoplastic manifestation of renal cell carcinoma (RCC) that is characterized by elevated alkaline phosphatase, erythrocyte sedimentation rate, α -2-globulin, and γ -glutamyl transferase, thrombocytosis, prolongation of prothrombin time, and hepatosplenomegaly, in the absence of hepatic metastasis and jaundice. A rare variant of this syndrome with jaundice has recently been described in 3 cases in the literature. We report a patient who presented with abdominal pain and cholestatic jaundice in whom RCC was incidentally found during initial workup. Jaundice and liver dysfunction resolved completely after surgical resection of the tumor. This case illustrates the protean manifestations of RCC, and the importance of considering Stauffer's syndrome and its variant in the differential diagnosis of anicteric and icteric cholestasis, which may allow early recognition and treatment of an underlying malignancy.

KEY WORDS: jaundice; cholestasis; renal cell carcinoma; Stauffer's syndrome.

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Malignancy-related cholestasis is usually secondary to mechanical obstruction of the biliary tract or widespread hepatic metastasis. However, some malignancies can cause cholestasis as part of their paraneoplastic syndrome. Nonmetastatic nephrogenic hepatic dysfunction syndrome without jaundice (Stauffer's syndrome) is a paraneoplastic manifestation that often appears as the initial clinical presentation of renal cell carcinoma and other malignancies, including bronchogenic carcinoma, leiomyosarcoma, and prostate adenocarcinoma.¹⁻³ We report a case of a 39-year-old woman with a rare cholestatic variant of Stauffer's syndrome owing to renal cell carcinoma, which was diagnosed during an evaluation for cholestatic jaundice.

CASE REPORT

A 39-year-old Nicaraguan female was admitted to the hospital with a 1-month history of worsening jaundice, pruritus, and right upper quadrant discomfort. She reported intermittent fever, nausea, decreased appetite, and darkening of her urine for

2 weeks before admission. Past medical history included hypertension and hyperlipidemia. She had no previous surgery. She denied any significant alcohol, tobacco, or drug abuse, and had no risk factors for human immunodeficiency virus or chronic viral hepatitis. Physical examination revealed an icteric patient with right upper quadrant tenderness and hepatosplenomegaly. There were no other significant physical findings.

Laboratory data revealed anemia, leukocytosis, elevated alkaline phosphatase, aspartate aminotransferase, total bilirubin, and prothrombin time, with decreased serum albumin level (see Table 1). Alcohol, acetaminophen, and other toxicology screens were negative. Serum creatinine and blood urea nitrogen were normal, and urinalysis did not reveal blood or leukocytes.

Ultrasound of the abdomen revealed hepatosplenomegaly (liver measured 18 cm and spleen measured 13 cm), without evidence of intrahepatic or extrahepatic biliary dilatation, cirrhosis, or ascites. The kidneys revealed no evidence of hydronephrosis, renal stones, or masses. Further evaluation regarding the etiology of her underlying liver disease was undertaken. Antimitochondrial antibody, antinuclear antibody, antismooth muscle antibody, antineutrophil cytoplasmic antibody, and serologies for acute and chronic viral hepatitis were negative. In addition, iron studies, serum ceruloplasmin level, and α -fetoprotein level were all normal. The patient continued to have fever up to 101.5°F. Blood and urine cultures were negative. She was started empirically on piperacillin/tazobactam. Computed tomographic (CT) scan of the abdomen revealed hepatosplenomegaly, and a 3.0 × 3.0 × 4.0 cm exophytic mass arising from the left kidney (see Fig. 1). A metastatic workup, including a CT scan with intravenous contrast of the chest, abdomen, and pelvis, revealed no evidence of metastatic disease.

The patient's clinical condition was stable, and she was discharged home with a plan to arrange for a radical nephrectomy. Her symptoms and laboratory values remained unchanged during the several weeks between her hospital discharge and surgery. She subsequently underwent left radical nephrectomy. Pathology revealed evidence of renal cell carcinoma of clear cell type, without evidence of vascular invasion or extracapsular extension (see Fig. 2). The patient had an uneventful operative course with complete resolution of symptoms by the third postoperative month, and repeat

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Table 1. Laboratory Values

	Preoperative	Postoperative
Hemoglobin (g/dL)	10	12.4
Hematocrit (%)	31.1	36.1
Leukocytes ($\times 10^3$ U/L)	13.7	6.8
Platelets ($\times 10^3$ U/L)	406	156
Total bilirubin (mg/dL)	16.8	1.4
Normal 0.2 to 1.3 mg/dL		
Direct bilirubin (mg/dL)	14.9	
AST (IU/L)	146	26
Normal 15 to 46 IU/liter		
ALT (IU/L)	24	40
Normal 7 to 56 mg/dL		
Alkaline phosphatase (IU/L)	219	146
Normal 38 to 126 IU/liter		
Total protein (mg/dL)	7.2	7.8
Albumin (mg/dL)	2.9	4.3
Prothrombin time (s) normal 11.4 to 14 s	15.8	13.9

AST, aspartate aminotransaminase; ALT, alanine aminotransaminase.

laboratory studies revealed normalization of her liver chemistries (see Table 1).

DISCUSSION

The incidence of renal cell carcinoma has been increasing over the past several decades. In 2004, it accounted for approximately 2% of all cancers and 2% of all deaths from neoplasms.⁴ The wide array of its unusual presenting symptoms has led some authors to label it as the "internist's tumor." The classic diagnostic triad of flank pain, palpable abdominal mass, and hematuria is present in less than 10% of patients.⁵ More often, this tumor presents with systemic and paraneoplastic symptoms that may not suggest the correct diagnosis: increased erythrocyte sedimentation rate, anemia, cachexia, weight loss, fever, hypercalcemia, polycythemia, amyloidosis, neuromyopathy, and abnormal liver function.⁶

Cholestasis is frequently seen in patients with malignancy. It may be because of external compression of the hepatobiliary tree by an enlarged lymph node, pancreatic, ampullary,

FIGURE 2. Kidney biopsy showing clear cell-type renal cell carcinoma class 2 (hematoxylin and eosin, original magnification $\times 300$).

gallbladder carcinomas, or widespread hepatic infiltration by hepatoma or metastatic carcinoma. Cholestasis can also be part of a paraneoplastic syndrome of certain malignant diseases, especially lymphomas, in the absence of primary or metastatic liver disease. Depending on the severity of the cholestatic process, patients can be icteric (with jaundice), or anicteric (without jaundice). Nonmetastatic nephrogenic hepatic dysfunction syndrome (Stauffer's syndrome) is a unique paraneoplastic manifestation of renal cell carcinoma that is usually manifested as anicteric cholestasis. This syndrome was originally described in 1961 by M. H. Stauffer, and is characterized by elevated alkaline phosphatase, erythrocyte sedimentation rate, α -2-globulin, and γ -glutamyl transferase, thrombocytosis, prolongation of prothrombin time, and hepatosplenomegaly, in the absence of hepatic metastasis.⁷ Since that time, several cases have been reported in the English literature, confirming this association. The underlying pathophysiology of this paraneoplastic manifestation is not fully understood; however, reports have suggested the possible role of interleukin-6 overexpression by the primary tumor.⁸ This manifestation is not unique to renal cell carcinoma. It has also been described in patients with leiomyosarcoma, angiosarcoma, malignant histiocytoma, prostate carcinoma, and bronchial adenocarcinoma.¹⁻³

A rare variant of the syndrome presenting initially with jaundice (icteric cholestasis) has recently been described in the literature (see Table 2). In 1997, Dourakis et al. described the first 2 cases of this variant. The first case was a 65-year-old woman with no preexisting hepatobiliary disease, who presented with jaundice, pruritus, and urinary hyperpigmentation. A 2.5 cm renal mass was found incidentally by CT scan of her abdomen. She underwent right nephrectomy, and renal clear cell carcinoma was confirmed by pathology. The patient had complete resolution of her clinical and liver function abnormalities after surgery. The second case was a 48-year-old male who presented with jaundice and urinary hyperpigmentation. A space-occupying lesion in the right kidney was found in a CT scan of his abdomen. He underwent right nephrectomy with complete resolution of his symptoms after surgery.⁹ In 2005, Giannakos et al.¹⁰ reported a 73-year-old male who presented with painless jaundice, pruritus, urinary hyperpigmentation, and hepatomegaly. A 3 cm mass was

FIGURE 1. Abdominal computed tomography scan showing a mass in the anterior aspect of the superior pole of the left kidney.

Table 2. Stauffer's Syndrome Variant Case Reports

	Case 1: 1997 Dourakis ⁹ , et al	Case 2: 1997 Dourakis ⁹ , et al	Case 3: 2005 Giannakos ¹⁰ , et al	Case 4: Current Report
Age	65	48	73	39
Sex	Female	Male	Male	Female
Fever	Absent	Absent	Absent	Present
Abdominal pain	Absent	Absent	Present	Present
Jaundice	Present	Present	Present	Present
Pruritus	Present	Absent	Present	Present
Hepatomegaly	Absent	Absent	Present	Present
Splenomegaly	Absent	Absent	Absent	Present
Urinary hyperpigmentation	Present	Present	Present	Present
Hemogram	Normal	Normal	Anemia	Anemia
Total bilirubin (mg/dL)	6.2	2.8	12.3	16.8
Direct bilirubin (mg/dL)	4.2	2.2	10.1	14.9
AST (IU/L)	158	132	127	146
ALT (IU/L)	426	334	82	24
Alkaline phosphatase (IU/L)	163	193	193	219
γ -glutamyl transferase (IU/L)	921	820	145	N/A
Renal biopsy	Clear cell type	Adenocarcinoma	Clear cell type	Clear cell type
Resolution	Complete	Complete	Complete	Complete

AST, aspartate aminotransaminase; ALT, alanine aminotransaminase.

found in the right kidney, and the patient underwent radical nephrectomy. Pathological examination confirmed the diagnoses of renal clear cell carcinoma, and the patient had complete normalization of his biochemical liver abnormalities. None of the above cases had evidence of metastatic disease.

Our patient's presentation had features that were consistent with the icteric variant of Stauffer's syndrome: hepatosplenomegaly, elevated alkaline phosphatase, decreased albumin, and prolonged prothrombin time, in addition to cholestatic jaundice. There was no evidence of liver metastasis by abdominal CT, and histological examination of the tumor revealed no renal vascular or capsular invasion. The improvement in the patient's clinical picture and the normalization of the laboratory parameters after tumor resection suggested Stauffer's syndrome with cholestatic jaundice as

the correct diagnosis. We think that our case adds to the growing pool of data of this rare variant of Stauffer's syndrome. Clinicians should be aware of this rare syndrome and its variant, and renal cell carcinoma should be included in the differential diagnosis of both icteric and anicteric cholestatic liver disease.

CONCLUSION

In a patient presenting with cholestatic jaundice without recognizable etiology, further evaluation for an underlying malignancy such as renal cell carcinoma should be considered. This is one of the diverse presenting manifestations of "the internist's tumor," and its recognition may lead to early diagnosis and improved outcome.

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