Hepatic Dysfunction in Renal Cell Carcinoma: A Stauffer Syndrome Variant

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Abstract

Cholestatic jaundice is usually linked to a malignant disease when it is secondary to a mechanical obstruction of the bile duct or due to hepatic metastasis. As a paraneoplastic syndrome, cholestasis has been described in lymphoproliferative disorders, in prostate cancer and as the Stauffer syndrome with non-metastatic dysfunction in patients with renal cell carcinoma (RCC). We present the case of a 61 year old patient with a paraneoplastic manifestation with cholestatic jaundice due to RCC with kidney and lung metastases. Clinical characteristics of patients with RCC vary and sometimes manifest in a peculiar way. Cholestatic jaundice is a rare paraneoplastic syndrome associated with RCC and with the exclusion of more frequent causes, it should be taken into account in the differential diagnosis. This rare but possible association requires prompt recognition, as prognosis correlates with disease stage and influences patient's overall survival, and an early recognition of this syndrome may improve, sometimes, patients' outcome.

Keywords: renal cell carcinoma, Stauffer Syndrome, jaundice

1. Introduction

Cholestatic jaundice is usually linked to a malignant disease if it is secondary to a bile duct mechanical obstruction or to

hepatic metastasis. As a paraneoplastic syndrome, cholestasis has been described in lymphoproliferative disorders [1], prostate cancer [2] and as the Stauffer syndrome with non-metastatic dysfunction in patients

with renal cell carcinoma (RCC) [3]. Also known as vanishing bile duct syndrome, it should be taken into consideration if a malignant disease has been previously diagnosed.

2. Case report

A 61 year old patient was admitted into our Gastroenterology Department for jaundice, pruritus, upper abdominal pain and fever. Symptomatology began almost a month previously with nausea, low appetite and fatigability. The symptoms considerably worsened during this period. During our medical interview, we found that the patient also had a type II diabetes and also underwent surgery for a stage II sigmoid adenocarcinoma 5 years before. He denied any other medical problems. He also denied using alcohol, tobacco or illicit drugs.

The physical examination was significant for an intense jaundice, tenderness in the upper abdominal quadrants and a hepatosplenomegaly. The vitals were completely normal. The laboratory results were significant for inflammatory markers, severe anemia and cholestasis. Acetaminophen levels, hepatitis A, B and C serologies, ceruloplasmin, α -fetoprotein level and antinuclear antibody profile were all within normal limits. Also, blood and urine cultures were negative.

A colonoscopy was performed and no lesions were found. An abdominal ultrasound showed hepatosplenomegaly,

with the liver's right lobe measuring 16 cm and the spleen approximately 17 cm. The gallbladder had small quantities of sediment. Further examination revealed on the left kidney a large hypoechoic mass of approximately 6 x 5 x 5 cm. The patient underwent a CT scan which confirmed the presence of a heterogeneously enhanced left renal tumor (Figure 1). No distant metastasis was present. The kidney was working properly, had no visible dilations, no vessel thrombosis, although the surrounding perirenal fat appeared infiltrated. The liver showed no intrahepatic dilations and no masses.

Fig 1. Left renal tumour on CT scan

Subsequently, given the fact that no signs of hepatic metastases were found and other possible cholestatic disorders were excluded, we directed the patient to the Oncology Department with the diagnosis of

paraneoplastic syndrome due to renal cancer. A left radical nephrectomy was performed with free tumor surgical margins. Pathology revealed a clear cell renal carcinoma, invading the perirenal fat, with no vascular involvement.

3. Discussions

Cancer related cholestatic jaundice is usually related to the main bile duct obstruction, widespread liver metastasis or secondary to a paraneoplastic syndrome [4]. Several malignant disorders such as bronchial adenocarcinoma, leiomyosarcoma, malignant histiocytoma, prostate cancer and RCC have been described as causes of cholestatic jaundice without liver metastases [5, 6, 7]. Renal cell associated paraneoplastic syndromes are relatively frequent, as almost 10 to 40% of patients diagnosed with RCC deviate from the classic triad of palpable mass, hematuria and flank pain [8]. An uncommon intrahepatic cholestatic syndrome (Stauffer's Syndrome) was originally described in 1961 by M.H. Stauffer and it usually manifests as anicteric cholestasis in the absence of hepatic metastases [3]. Several cases have been published so far, that associate hepatosplenomegaly, fever, weight loss, with elevated liver enzymes, high erythrocyte sedimentation rate and abnormal liver function tests with no other obvious cause of cholestasis than renal cancer [9,10]. The underlying mechanism of paraneoplastic cholestasis is not clear yet.

However, several theories suggested that it may be caused by the tumor cells that secrete hepatotoxic substances which generate an autoimmune cross reaction by activating T cells and producing antibodies against liver antigens and, in a final stages, may also lead to hepatic injury. Also, interleukin-6 has been incriminated due to its capacity to stimulate hepatic protein production [8]. The only successful treatment consists in a nephrectomy. Subsequent elevation of hepatic enzymes after nephrectomy usually suggests a local or distal relapse [11].

In our case the patient presented with both cholestatic and systemic symptoms. Jaundice, pruritus, dark urine supported the cholestasis diagnosis, while other more general symptoms such as weight loss, fatigability might have been associated with the existing diabetes. The differential diagnostic of fever was: infection, inflammatory disease or malignancy.

All direct mechanical causes directly obstructing the biliary tree were excluded and no other causes of intrahepatic cholestasis were found. Common causes of hepatitis such as alcohol or viral hepatitis were ruled out and we also excluded acetaminophen intoxication, infectious disease, primary biliary cirrhosis or other immunological disease as all the laboratory tests were normal. On the other hand, imaging investigations showed several hypoechoic masses on the left kidney which suggested a renal cancer. Although alkaline

phosphatase and γ -glutamyltransferase levels were elevated at presentation, no clinical hyperbilirubinemia was present. Additionally, no other laboratory abnormalities were observed, and following nephrectomy, the patient's status improved with liver serum enzymes decreasing significantly.

Interleukin 6 (IL-6) is considered an autocrine growth factor with effect on liver cells, and is part of the inflammatory inflammation response to tissue injury. The IL-6 increase in Stauffer's syndrome IL-6 may represent an acute inflammatory reaction caused by the liver infiltration by immune cells [12,13].

RCC is well known for its variety of paraneoplastic symptoms and has been labeled "the internist tumor". Together with hypercalcemia, polycythemia, coagulopathy, amyloidosis, vasculopathies, neuromyopathies, non-metastatic hepatic dysfunction has

been described as a paraneoplastic syndrome in the context of the initial diagnostic of renal cancer, or relapse after nephrectomy [8].

4. Conclusion

Clinical characteristics of patients with RCC vary and sometimes manifest in peculiar ways. RCC may present as cholestatic jaundice, and after excluding more frequent causes, a rare paraneoplastic syndrome should be taken into account in the differential diagnosis of icteric liver disease. This rare but possible association requires prompt recognition, as prognosis correlates with disease stage and, therefore, an early recognition of this syndrome may improve, sometimes, patients' outcome.

Abbreviations

IL-6 – Interleukin 6

RCC – renal cell carcinoma

Statements

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