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CASE REPORT | LIVER

Paraneoplastic Hepatopathy Associated with Gastrointestinal Carcinoid

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ABSTRACT

Paraneoplastic hepatopathy has been reported with various malignancies, most commonly with renal cell cancer. This non-metastatic hepatic dysfunction in such malignancies is known as Stauffer syndrome. We describe a 61-year-old man who presented with symptoms of bowel obstruction with marked cholestasis and high levels of alkaline phosphatase and bilirubin. Imaging revealed an unremarkable liver and a mass in the ileocecal valve with mesenteric lymphadenopathy. Biopsies were consistent with a carcinoid tumor. Liver dysfunction gradually resolved after surgical resection of the tumor. Paraneoplastic syndrome should be considered in the differential diagnosis for patients with carcinoid tumors who present with cholestasis.

INTRODUCTION

Carcinoid tumors are a type of slow-growing neuroendocrine tumors, usually arising from the gastrointestinal (GI) tract anywhere between the stomach and rectum. The small bowel is the most common site of carcinoid within the GI tract.[1] These tumors have a predilection to metastasize to the liver, frequently affecting both lobes. Wide dissemination throughout the liver has been reported occasionally.[2] Paraneoplastic liver dysfunction, although an extremely rare phenomenon, has been described with various malignancies, most commonly with renal cell cancer and lymphoma.[3-6]

CASE REPORT

A 61-year-old man with a known history of hypertension and gastroesophageal reflux disease presented to the emergency room with worsening abdominal pain, intractable nausea, and 3 days of vomiting. He was experiencing episodes of nonspecific abdominal pain that would last for 4–5 days every month for the previous year. Over-the-counter medications such as ranitidine and magnesium oxide provided minimum relief. Prior to admission, the patient took 4 tablets of 81-mg aspirin and 9 tablets of 250-mg acetaminophen over 3 days. Review of systems was positive for intermittent constipation, heartburn, and anorexia. He denied use of alcohol and herbal medications or supplements. Vital signs at the time of triage were stable.

Physical examination was significant for scleral icterus, jaundice, and tenderness in the epigastrium and right lower quadrant of the abdomen. Laboratory data revealed a normal white blood cell count and platelet count, with hemoglobin 16.1 g/dL. The liver enzymes were remarkable for total bilirubin 10.6 mg/dL, conjugated bilirubin 7 mg/dL, alanine aminotransferase (ALT) 371 IU/L, aspartate aminotransferase (AST) 252 IU/L, gamma-glutamyl transpeptidase 301 IU/L, and alkaline phosphatase 199 IU/L. Serological tests for viral hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, and herpes virus were negative. Acetaminophen, salicylate, and ethanol levels were undetectable. Autoimmune disease was also ruled out by negative immunological assays.

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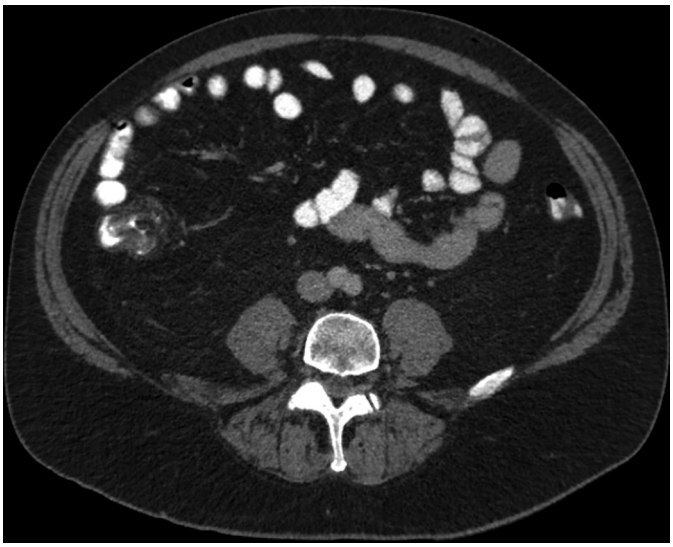

Figure 1. Computed tomography showing a partially calcified ileocecal mass.

During the course of his admission, his aminotransferases rose gradually, peaking at 512 IU/L AST and 593 IU/L ALT at hospital day 11. Total bilirubin trended down slightly to 7.2 mg/dL. Computed tomography (CT) of the abdomen with contrast performed in the emergency room revealed a 2 cm x 3 cm calcified speculated mass located in the ileocecal valve with associated right lower quadrant mesenteric lymphadenopathy and an unremarkable liver, spleen, and pancreas (Figure 1). Repeat CT of the chest/abdomen/pelvis performed as part of the metastatic work-up at our institute revealed findings similar to the prior CT imaging. Tumor markers carcinoembryonic antigen and alpha-fetoprotein were negative. The patient refused magnetic resonance imaging due to severe claustrophobia. An upper endoscopy revealed a segment of Barrett's esophagus Prague Classification C8M9, with gastroesophageal junction 38 cm from the incisors; biopsies confirmed goblet cell metaplasia consistent with Barrett's esophagus. A colonoscopy revealed evidence of a submucosal mass in the ileocolonic region/terminal ileum, which was obstructing the terminal ileum (Figure 2). The biopsies of the mass were consistent with carcinoid tumor (Figure 3). An octreotide scan revealed focal radiotracer uptake within the partially calcified soft tissue mass that abutted and involved the medial wall of the cecum. There was an additional focus of radiotracer uptake in a soft tissue mass within the mesentery adjacent to the cecal mass, which represented a lymph node. There was a physiologic distribution of radiotracer uptake in the liver but no evidence of metastasis (Figure 4).

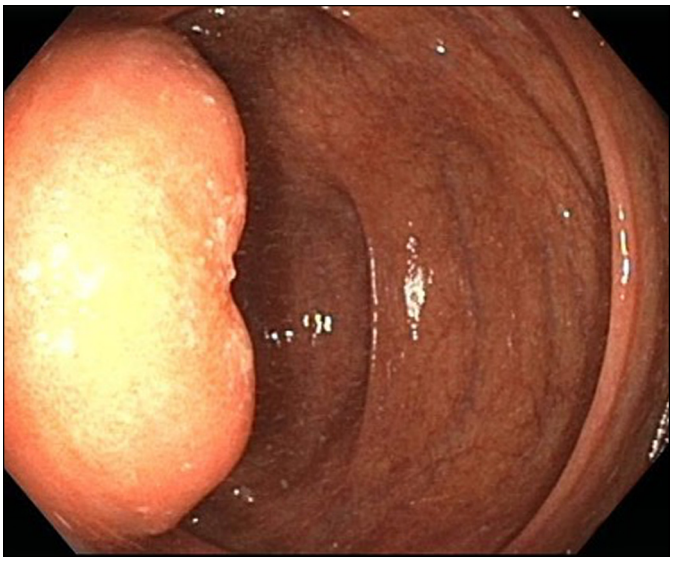

Figure 2. Colonoscopy showing a partially obstruction, likely a submucosal ileocecal mass.

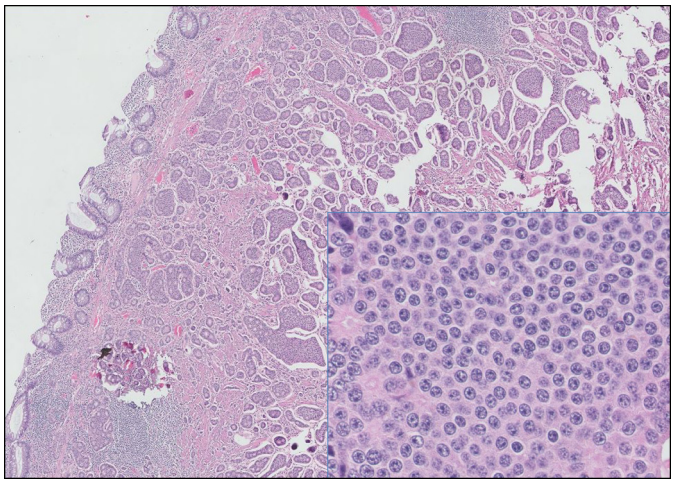

Figure 3. Biopsy staining was positive for chromogranin, synaptophysin, and pancytokeratin, consistent with carcinoid.

The ileocecal mass was surgically resected, along with lymph node dissection. Final surgical pathology revealed a low-grade neuroendocrine tumor (carcinoid), 1.5 cm in the largest dimension, infiltrating through the muscularis propria to the subserosal adipose. Seven of the 12 lymph nodes resected were positive for metastatic carcinoma. The margins of the resection were negative. The appendix was negative for neuroendocrine tumor. Tumor cells were positive for chromogranin, synaptophysin, and pan-cytokeratin (AE1/AE3), and negative for CD56 and TTF-1. Ki-67 labeling index was $\leq$2%. The liver abnormalities without a discernable cause called for a liver biopsy, which showed benign liver parenchyma.

After the surgical resection of the tumor, the liver enzymes trended down and normalized within 2 weeks. The absence of any definite cause of cholestasis in conjunction with immediate downward trending of liver enzymes after resection of the carcinoid suggests a paraneoplastic phenomenon.

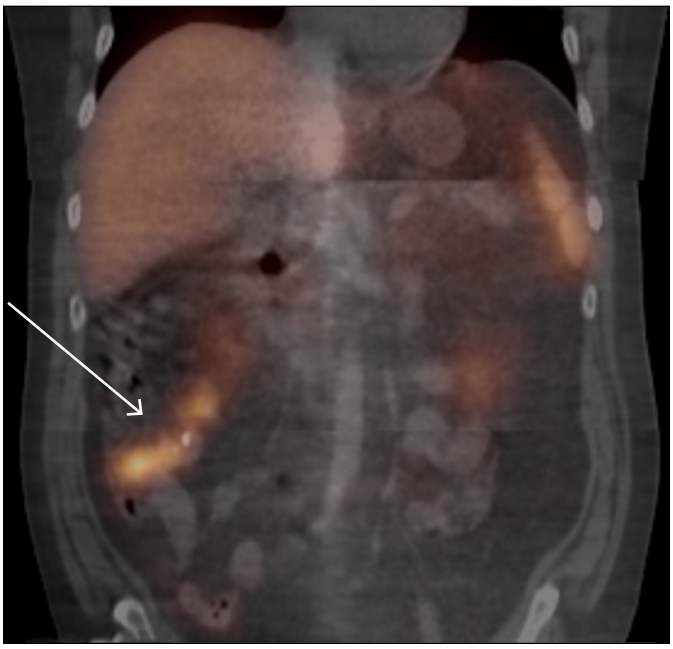

Figure 4. Octreotide scan showing focal radiotracer uptake at the ileocecal region with adjacent lymph node uptake.

DISCUSSION

Intrahepatic cholestasis as a paraneoplastic phenomenon was first described by M.H. Stauffer in patients with renal cell carcinoma in 1961, and it became popularly known as Stauffer syndrome or nephrogenous hepatosplenomegaly. Patients with Stauffer syndrome present with jaundice, fever, and hepatosplenomegaly, as well as elevated levels of alkaline phosphatase, erythrocyte sedimentation rate, γ-glutamyl transferase, alpha globulins, and thrombocytosis, and low albumin levels.[7] Non-specific inflammation, rare granulomas, and sinusoidal dilation of the liver is seen histologically.[8] These findings subside after tumor resection and recur with tumor recurrence. Presence of the syndrome postoperatively correlates with poor prognosis.[9]

Paraneoplastic hepatopathy/cholestasis has been described most commonly with renal cell carcinomas and lymphomas.[3-7] Rare cases have also been reported with T cell lymphoma, pheochromocytoma, prostate adenocarcinoma, sarcoma, ovarian dysgerminoma, and medullary thyroid cancer.[5,10-14]

The underlying pathogenesis of paraneoplastic liver dysfunction is not fully understood; however, reports have postulated a possible role of increased expression of inflammatory cytokines. Blay et al[15] demonstrated that interleukin-6 (IL-6) is involved in the pathophysiology of paraneoplastic syndromes in patients with metastatic renal carcinoma. Increased IL-6 was found in patients with increased C-reactive protein, haptoglobin, paraneoplastic cholestasis, paraneoplastic thrombocytosis, neutrophilia, and monocytosis.In a recent case report of paraneoplastic cholestasis associated with ovarian dysgerminoma, the tumor stained positive for TNF-α and negative for IL-1, IL-2, and IL-6, which suggests the presence of cytokines other than IL-6 in the pathogenesis.[13] In another report where the primary diagnosis was pheochromocytoma, IL-1β was postulated in the pathogenesis of intrahepatic cholestasis.[10] These findings suggest that multiple cytokines may be involved in different malignancies. The exact mechanism, however, has not yet been elucidated.

This is the first case of paraneoplastic hepatopathy seen in a carcinoid tumor and can be considered as a variant of Stauffer's syndrome. It is a rare phenomenon with an unclear pathophysiology. Our case adds to the growing pool of data of this rare syndrome.

DISCLOSURES

Author contributions: D. Mehta wrote the case report, provided the images, and is the article guarantor. P. Chugh provided the radiological images and edited the manuscript. L. Chawla wrote the manuscript. D. Jodorkovsky edited the manuscript.

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