

# Vanishing Bile Duct Syndrome in a Patient with Uterine Cancer and Paraneoplastic Systemic Sclerosis

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## ABSTRACT

Vanishing bile duct syndrome (VBDS) is a rare entity of acquired disorders resulting in cholestasis secondary to progressive destruction of intrahepatic bile ducts. The syndrome has been described in the setting of autoimmune disorders, medication toxicities, genetic disorders, infectious etiologies, and in rare cases, neoplastic processes. There are no known case reports of VBDS in the setting of uterine malignancy. We present a case of VBDS in a patient with underlying uterine cancer complicated by paraneoplastic systemic sclerosis.

## INTRODUCTION

Vanishing bile duct syndrome (VBDS) refers to a group of acquired disorders characterized by progressive obliteration of the biliary tree. The acquired loss of intrahepatic bile ducts that occurs in VBDS has been described in the setting of immunologic, ischemic, infectious, metabolic, and toxic processes.<sup>1</sup> Rarely, VBDS has been described in the setting of neoplastic disorders, namely in association with Hodgkin's lymphoma.<sup>2</sup>

## CASE REPORT

A 55-year-old Caucasian woman with hypertension was admitted to an outside hospital for progressive dyspnea and lower-extremity edema for the prior 2 months. She denied chest pain, abdominal pain, nausea, and gastrointestinal symptoms. Review of symptoms was negative for skin changes, orthopnea, fevers, weight loss, and night sweats. She was a lifetime nonsmoker, and she reported social alcohol use with less than 2 alcoholic beverages per month. Home medication included losartan 50 mg daily. Initial workup included basic labs and a computed tomography (CT) scan of the chest, abdomen, and pelvis with contrast ordered by the emergency room physician. Labs revealed elevated liver function tests (LFTs) with elevated alkaline phosphatase (ALP) >500 U/L, mildly elevated aspartate transaminase (AST) and alanine transaminase (ALT), and international normalized ratio 1.16. The CT scan of the chest, abdomen, and pelvis revealed a uterine mass. Subsequent biopsy yielded a diagnosis of endometrial carcinoma. Prior to discharge, her hospital workup included a negative hepatitis panel, normal iron studies, and negative smooth muscle antibody. Right upper quadrant ultrasound was unremarkable.

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While undergoing outpatient evaluation for surgical management of the uterine carcinoma, the patient was again found to have elevated ALP (714 U/L) and elevated transaminases (aspartate aminotransferase 120 U/L, alanine aminotransferase 94 U/L). Total bilirubin was found to be 1.5 (direct bilirubin 0.8 mg/dL); international normalized ratio was 1.2. Workup revealed negative liver-kidney microsomal antibody, antimitochondrial antibody, and anti-smooth muscle antibody. She was found to have normal ceruloplasmin and alpha-1 antitrypsin levels. Antinuclear antibody was elevated at 1:160. The patient was referred for a core liver biopsy 1 month following her initial presentation. Tissue was analyzed with specialized stains using periodic acid-Schiff with and without diastase, trichrome, reticulin and iron, and CK7.

Liver biopsy revealed marked ductal reaction and mild focal cholestasis suggestive of biliary obstruction (Figure 1). Evaluation of tumor markers revealed normal  $\alpha$ -fetoprotein and carcinoembryonic antigen. Cancer antigen-125 and carbohydrate antigen 19-9 were elevated at 101.9 and 67.8, respectively, consistent with her diagnosis of uterine malignancy. Positron emission tomography showed a hypermetabolic primary uterine malignancy with abdominopelvic lymph node metastases. Liver and gallbladder were within normal limits.

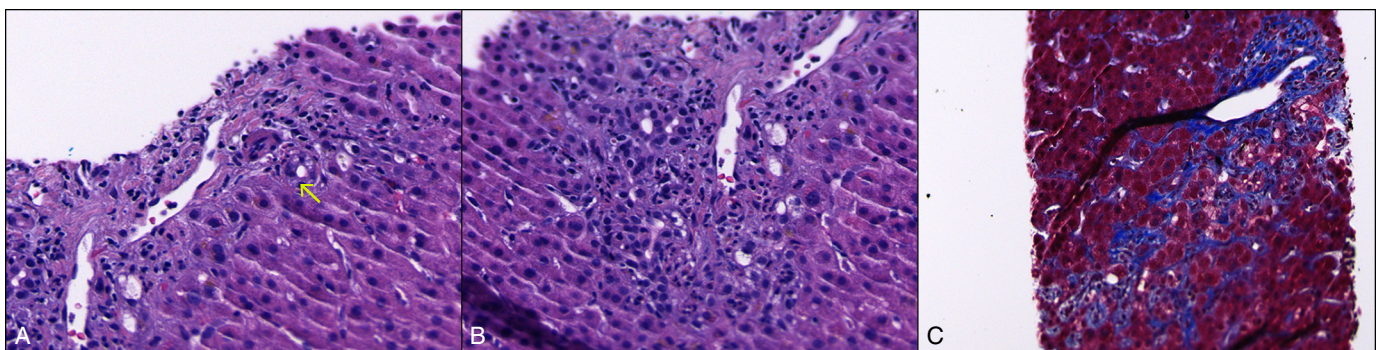
Two months following her initial presentation, the patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy with tumor debulking, lymph node resection, and infracolic omentectomy. She was surgically staged with FIGO I stage III C2 endometrial adenocarcinoma. The tumor was metastatic to iliac, para-aortic, and pelvic lymph nodes.

Liver chemistries were again noted to be abnormal on this admission, and gastroenterology was consulted. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) were recommended to further evaluate her abnormal LFTs. Due to postoperative acute kidney injury believed to be of pre-renal etiology, the tests were

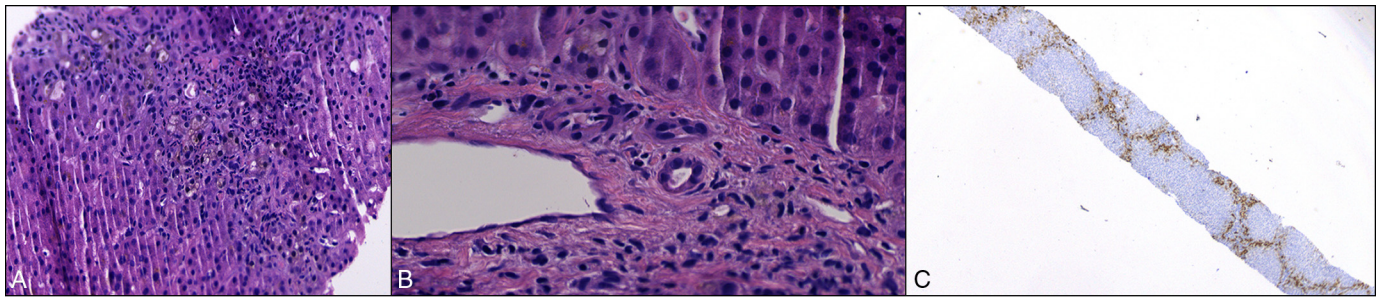
not performed. The patient was discharged home with instructions to follow up for an outpatient MRI/MRCP.

Two weeks after surgery, the patient was readmitted to the hospital for an acute rise in LFTs and worsening creatinine noted upon outpatient follow-up. Admission laboratory values were significant for ALP 2,188 U/L, AST 338 U/L, ALT 113 U/L, total bilirubin 4.5 mg/dL, direct bilirubin 3.6 mg/dL, international normalized ratio 1.24, and creatinine 1.8 mg/dL. At this time, the patient had new complaints of skin jaundice, bilateral hand pain with distal skin tightening, and “blue fingers” suggestive of Raynaud’s phenomena. Physical exam revealed scleral icterus and diffuse jaundice. Examination of her hands revealed sclerodactyly and ulcerations of her digital pits. A gastrointestinal specialist was again consulted for her abnormal liver chemistries and rheumatology for evaluation of her new historical and physical complaints. Workup revealed positive anti-centromere and anti-RNA polymerase II antibodies. At this time, the patient was diagnosed with scleroderma, thought to be paraneoplastic in nature. Given the diagnosis of scleroderma, the differential for her abnormal liver chemistries broadened to consider autoimmune etiologies, including autoimmune hepatitis and primary biliary cirrhosis (PBC). The patient underwent repeat liver biopsy and was empirically started on oral prednisone 40 mg daily for autoimmune hepatitis.

On follow-up, the patient’s LFTs showed no improvement, and she was referred for endoscopic retrograde cholangiopancreatography (ERCP) for evaluation of possible extrahepatic biliary obstruction. ERCP ruled out stricture or obstruction and cholangiography was normal. Approximately 2 weeks later, she was readmitted to the hospital with acute creatinine elevation to 4.6 mg/dL. Suspicion was high at this time for scleroderma renal crisis in the setting of recent corticosteroid use. Admission laboratory values were significant for ALP 602 U/L, AST 101 U/L, ALT 47 U/L, total bilirubin 11.6 mg/dL, and international normalized ratio 1.46. She developed hypertensive crisis, flash pulmonary edema, and hypoxic respiratory failure requiring intubation. Prednisone was



**Figure 1.** (A) Hematoxylin and eosin (H&E) stain of portal tract ( $\times 200$ ) with mild duct injury (arrow), cholangiolar cholestasis, and ductal reaction. (B) H&E stain ( $\times 400$ ) showing extensive mixed inflammation including leukocytes. (C) Trichrome stain ( $\times 200$ ) showing mild periportal fibrosis.



**Figure 2.** (A) Hematoxylin and eosin (H&E) stain ( $\times 200$ ) showing more advanced cholestasis, mixed inflammation, and loss of bile ducts. (B) H&E stain ( $\times 400$ ) showing senescent-type degenerative changes in bile ducts. (C) Cytokeratin 7 immunohistochemical stain ( $\times 20$ ) showing extensive ductular reaction.

discontinued, and she was started on captopril for presumed scleroderma renal crisis. She began regular hemodialysis for volume overload and was later extubated. Renal biopsy demonstrated changes consistent with scleroderma renal disease characterized by thrombotic microangiopathy involving arteries and arterioles. Bile cast nephropathy was also noted as a consequence of her liver disease.

Independent review of the patient's second liver biopsy by two pathologists revealed moderate ductal reaction with cholestasis. Progressive ductopenia was seen in 15 of 22 portal tracts, in addition to increased portal expansion and fibrosis (Figure 2). VBDS was diagnosed in the setting of uterine cancer complicated by paraneoplastic scleroderma. The patient was discharged once she was stabilized, and she followed up as an outpatient for routine monitoring of LFTs. The patient was continued on long-term dialysis and follow-up for her malignancy care.

## DISCUSSION

VBDS is a rare and poorly understood entity characterized by progressive "ductopenia," or loss of intrahepatic bile ducts. Among patients who acquire ductopenia, clinical outcomes vary depending on patient characteristics and underlying etiology, ranging from significant biliary epithelial regeneration and clinical recovery to progressive duct loss, cholestasis, hepatic fibrosis, cirrhosis, and ultimately death.<sup>1</sup> As previously described, ductopenia and VBDS have well-recognized associations with autoimmune disorders, medication toxicities, genetic abnormalities, infectious diseases, and neoplastic disorders. Review of the literature surrounding neoplastic associations is notable primarily for a rare but well-established presentation of Hodgkin's lymphoma in which liver infiltration by lymphoma cells results in bile-duct loss and cholestasis.<sup>2,3</sup> Langerhans cell histiocytosis and hemophagocytic lymphohistiocytosis have also been loosely associated.<sup>4,5</sup> However, to our knowledge there are no reported cases of uterine cancer with concomitant paraneoplastic ductopenic liver involvement.

This intricate case describes a patient who developed VBDS in the setting of uterine cancer complicated by paraneoplastic scleroderma. We argue that VBDS developed as a second paraneoplastic manifestation of her uterine carcinoma.

It has come to our attention that forming a definitive association between uterine carcinoma and VBDS is complicated in this case by the patient's diagnosis of possible paraneoplastic scleroderma, a rare immunological entity in itself. As previously discussed, immunologic disorders may be associated with bile duct loss and therefore could have contributed to this patient's ductopenia and VBDS. While scleroderma has not been independently associated with ductopenia or VBDS, PBC is the most common cause of adult ductopenia and, in addition, may rarely be associated with scleroderma and systemic sclerosis.<sup>6,7</sup> Our patient did not fit diagnostic criteria for PBC, with negative antimitochondrial antibody and an absence of characteristic features on liver biopsy.<sup>8</sup> Primary sclerosing cholangitis (PSC), yet another known immunologic cause of ductopenia<sup>6</sup>, was also considered in the differential diagnosis, but it was deemed less likely in this case given normal ERCP and cholangiogram.<sup>6,9</sup> Sarcoidosis has also been linked to ductopenia, but classic findings of noncaseating granulomas were not seen on liver biopsy, and the patient demonstrated no pulmonary pathology.<sup>6,10</sup>

Further workup did not suggest the presence of any other diseases previously associated with VBDS or those with common liver manifestations. Liver-kidney microsomal antibody and anti-smooth muscle antibody were negative, making autoimmune hepatitis an unlikely diagnosis. Ceruloplasmin and alpha-1 antitrypsin levels were within normal limits, further ruling out Wilson's disease or alpha-1 antitrypsin deficiency. Iron studies were normal, making hemochromatosis unlikely. Finally, viral hepatitis panels were negative, ruling out infectious viral hepatic disease.

Given clinical findings excluding other established and potential causes of ductopenic liver disease, it seems probable that this patient's VBDS was a paraneoplastic disorder secondary to her uterine carcinoma. A paraneoplastic phenomenon is

simply a clinical outcome secondary to the products of a tumor or the body's reaction to a tumor. Uterine cancer has been described in the literature in association with other paraneoplastic syndromes including palmoplantar keratoderma, the Leser-Trélat sign (considered a cutaneous paraneoplastic syndrome), pemphigus, and possibly sensory neurological dysfunction.<sup>11-14</sup>

Data suggest that proteins involved in the regulation of cellular apoptosis (BCL-2, which inhibits apoptosis, and BAX, which promotes apoptosis) may be integrally involved in the pathogenesis of both uterine cancer and VBDS. While not completely understood, the pathophysiology of VBDS is believed to be related to biliary apoptosis, specifically with dysregulation between BCL-2 and BAX, resulting in interlobular bile duct destruction with excessive apoptosis and insufficient regeneration.<sup>1</sup> Interestingly, in a study exploring the pathogenesis of uterine cancer, results showed a paradoxically lower BCL-2/BAX ratio in endometrial carcinoma compared to normal endometrium, favoring apoptosis in the setting of over-proliferation of cells.<sup>15</sup> Overall, this indicates a loss of control of cell homeostasis as an important underlying cause of endometrial proliferation and uterine cancer. This commonality of apoptotic dysregulation may support a relationship between endometrial carcinoma and VBDS, as well as an immunologic mechanism for their association.

Prognostication and the development of a treatment plan for VBDS is complex because the underlying cause remains poorly understood. Currently, treatment is targeted toward the underlying etiology. Ursodeoxycholic acid (UDCA), a synthetic bile salt, is critical in supportive care, and it is often given at high doses (eg, 45 mg/kg per day).<sup>16,17</sup> Because etiologies of VBDS are often related to immunologic causes, immunosuppression has been proposed as a potential treatment; however there is minimal evidence supporting its use.<sup>18</sup> Patients with severe progression with liver decompensation should be considered for liver transplantation because there are case reports of successful transplantation without recurrence.<sup>19,20</sup>

In this case, prognosis and treatment are clearly challenging. The subtlety of bile-duct loss on the initial liver-biopsy specimen resulted in a substantial delay in identifying the cause of the patient's jaundice. The patient had 2 liver biopsies within a 2-month time frame that showed relatively rapid progression of bile duct loss. The significance of the tempo of disease progression is unknown, but we presume it to be a poor prognostic factor. Disease usually occurs subacutely in cases of described ductopenia. In addition, this patient's LFTs and bilirubin worsened despite treatment of the underlying uterine cancer, and her poor functional status precluded the initiation of chemotherapy. Considering these factors, initiation of high-dose UDCA was the recommended therapy. Liver transplant was not recommended given her prognosis from her

malignancy complicated by renal failure from paraneoplastic scleroderma.

In summary, this case highlights an exceedingly rare case of VBDS and paraneoplastic scleroderma in the setting of a uterine malignancy, with no similar cases identified in the literature. Given the extreme rarity of this condition, the diagnosis, prognosis, and treatment plan proved difficult, creating a dilemma for both the patient and her care providers. Outcomes from further case reports may help elucidate etiology or best treatment in similar cases.

This case shows that VBDS should be considered in cases of persistently elevated liver enzymes without an obvious source, especially in the setting of malignancy or immunologic disorders.<sup>2</sup> Finally, this case presents an opportunity to explore the link between VBDS and the imbalance between pro- and anti-apoptotic factors associated with uterine and other malignancies as a potential paraneoplastic mechanism.

## DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. D. Sedhom is the article guarantor.

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