Resolution of Diffuse Intrahepatic Biliary Strictures after Chemotherapy for Metastatic Ovarian Cancer

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ABSTRACT

Sclerosing cholangitis and cholestatic jaundice secondary to metastatic disease is a rare complication. We report a rare case of secondary sclerosing cholangitis (SSC) due to lymphatic spread from ovarian cancer with complete resolution after chemotherapy. The diagnosis of SSC from metastatic ovarian cancer was clinically challenging, as endoscopic retrograde cholangiopancreatography revealed irregular hepatic ducts consistent with sclerosing cholangitis, but it did not identify any malignant cells. The final diagnosis was made with liver biopsy revealing high-grade metastatic Mullerian carcinoma. The patient responded well to chemotherapy and is in remission. A timely diagnosis is important and can lead to complete resolution of the disease.

INTRODUCTION

Sclerosing cholangitis is a chronic and progressive cholestatic disease characterized by inflammation, fibrosis, and stricturing of the bile ducts. The majority of cases are idiopathic, known as primary sclerosing cholangitis (PSC).[1] A small number of patients are diagnosed with secondary sclerosing cholangitis (SSC) caused by metastatic disease, infection, ischemia, autoimmune dysfunction, obstruction, and toxins.[1,2] The prognosis of SSC depends on the timing of diagnosis and the underlying etiology. The definitive treatment for advanced cases is liver transplantation.[3]

CASE REPORT

A 53-year-old woman with a history of *BRCA2* stage III recurrent ovarian cancer presented with complaints of abdominal pain for the past 3 weeks. She characterized the pain as burning and mid-epigastric, radiating to the back and right shoulder. Pain progressed from intermittent during the initial few days to constant in the past week. Eating did not exacerbate or alleviate the pain. Associated symptoms included yellowing of the eyes and skin, nausea with non-bilious and non-bloody vomiting, and generalized fatigue for the past 3 days. She denied pruritis, bowel habit changes, fevers, chills, night sweats, or recent travel. There was no personal or family history of hepatobiliary disease.

Eight weeks prior, the patient was hospitalized for similar symptoms. Liver serologies showed aspartate transaminase 2,585 U/L, alanine transaminase 3,545 U/L, alkaline phosphatase 162 U/L, and total bilirubin 7.3 mg/dL. Workup for viral, autoimmune, and ischemic hepatitides was non-revealing. Two months prior, the patient was diagnosed with her second recurrence of ovarian cancer to the lymph nodes in the porta hepatis, retroperitoneum, and mediastinum, and she was started on olaparib (Lynparza, AstraZeneca Pharmaceuticals LP, Wilmington, DE), a poly-ADP ribose polymerase inhibitor approved by the U.S. Food and Drug Administration (FDA). Drug-induced liver injury was considered, but discontinuation of olaparib resulted only in transient improvement in symptoms

Figure 1. ERCP showing a long segment stricture of the left hepatic bile duct. Multiple irregular intrahepatic ducts are also visible in the right intrahepatic duct, suggestive of sclerosing cholangitis.

Figure 2. Microscopic image of liver biopsy showing tumor infiltration involving the portal lymphovascular spaces, consistent with high-grade metastatic Mullerian carcinoma. Hemotoxylin and eosin stain was used at 400x magnification.

and serologies. Imaging did not reveal any new signs of focal metastasis or liver abnormality. The patient improved with conservative management and did not resume olaparib. Liver serologies at discharge showed aspartate transaminase 2,145 U/L, alanine transaminase 1,299 U/L, alkaline phosphatase 120 U/L, and total bilirubin 5.3 mg/dL.

On her current admission, liver serologies showed aspartate transaminase 78 U/L, alanine transaminase 70 U/L, alkaline phosphatase 438 U/L, and total bilirubin 10.9 mg/dL. Magnetic resonance cholangiopancreatography did not show any discrete mass, but it did reveal mild dilatation of the intrahepatic biliary ducts in the left lobe and a hyperintense signal at the portal hepatis and portal triads, suggestive of an infiltrative process. Subsequent endoscopic retrograde cholangiopancreatography (ERCP) revealed irregularities of the extrahepatic bile ducts, a thickened common hepatic duct, and multiple irregular intrahepatic ducts with strictures suggestive of sclerosing cholangitis. The left main intrahepatic duct also showed a long segment stricture with upstream dilation, and a stent was placed (Figure 1). Bile duct biopsy showed atypical cells without evidence of malignancy. Despite stenting, liver serologies worsened: aspartate transaminase 167 U/L, alanine transaminase 104 U/L, alkaline phosphatase 641 U/L, and total bilirubin 17.5 mg/dL.

Transjugular liver biopsy then revealed high-grade metastatic Mullerian carcinoma involving the portal lymphovascular spaces with cholestasis and features of duct obstruction (Figure 2). The CA-125 level was 899 U/mL (normal <35 U/mL). After 3 months of treatment with cisplatin, her clinical symptoms resolved and liver serologies normalized: aspartate transaminase 30 U/L, alanine transaminase 29 U/L, alkaline
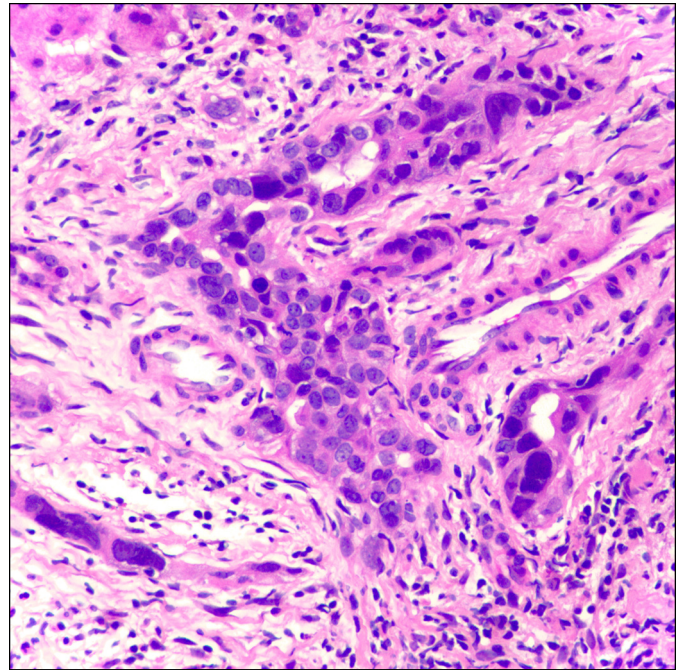
phosphatase 78 U/L, and total bilirubin 0.6 mg/dL. Repeat ERCP for stent removal also showed resolution of bile duct irregularities (Figure 3). Eight months after chemotherapy, the patient is in remission without evidence of recurrent liver abnormalities.

DISCUSSION

The constellation of symptoms and workup are consistent with SSC caused by metastatic disease. SSC can occur with drug-induced liver injury, although olaparib has not been shown to be hepatotoxic.[4] To our knowledge, only one case that documents SSC caused by ovarian cancer has been reported.[5] Unlike our patient, however, that patient had focal areas of liver metastasis and ultimately required surgery.[5]

Studies analyzing disease prevalence of SSC are limited. A study from the Mayo Clinic identified 31 cases over a 10-year period.[6] Etiologies of SSC include infection, ischemia, autoimmune dysfunction, obstruction, and toxins.[1,2] SSC has also occurred in cases of metastatic disease of the ovaries, prostate, gallbladder, pancreas, and colon/rectum.[5,7-9] Approximately half of patients with SSC are asymptomatic, but common clinical manifestations include generalized fatigue and pruritus.[10] Abdominal pain, fever, and jaundice can also occur with cholestasis or cholangitis.[11]

The diagnosis of SSC is supported with liver serologies showing elevated alkaline phosphatase and cholestasis. Imaging
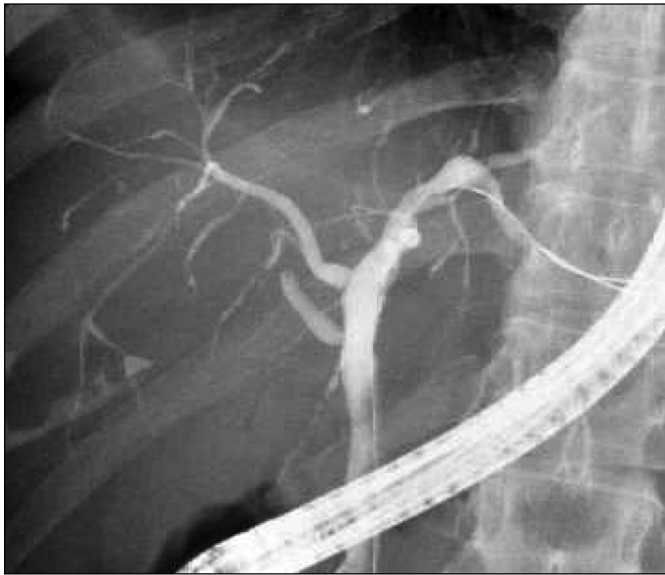
Figure 3. Repeat ERCP 2 months after the initiation of chemotherapy, showing resolution of intrahepatic duct irregularities.

can be helpful, but ultimately ERCP is the gold standard and can reveal multifocal stricturing and dilation of bile ducts that can present with intermittent segments of normal duct size to produce the characteristic bead-like appearance.[2] Liver biopsy is not required; however, if clinical suspicion of SSC is high, it should be performed immediately.[12]

Ursodeoxycholic acid is the mainstay of medical management, but it has not been shown to improve mortality or reduce the need for liver transplantation.[10,13] Future therapies include obeticholic acid, which was recently approved by the FDA to treat primary biliary cholangitis.[14] It is currently under study in a placebo-controlled trial for PSC (ClinicalTrials.gov Identifier: NCT02177136), but there are no studies evaluating the use of obeticholic acid with SSC. Endoscopic therapy for SSC is not well studied, and results are equivocal.[15,16] Early diagnosis of SSC can lead to prompt intervention and complete resolution.[1] When patients progress to end-stage liver disease, liver transplantation is the treatment of choice.[3] Without transplantation, the overall survival of patients with SSC compared to those with PSC was reduced by up to 17 months.[6]

To our knowledge, we report the first case of SSC as a result of metastatic disease from a primary ovarian carcinoma with complete resolution after chemotherapy. SSC is a rare disease that can be fatal if not diagnosed early. Differentiating SSC from other similar conditions is difficult though important, as early identification of SSC results in significant changes in management and prognosis.

DISCLOSURES

REFERENCES

1. Abdalian R, Heathcote EJ. Sclerosing cholangitis: A focus on secondary causes. *Hepatology*. 2006;44:1063–74.
2. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010;51:660.
3. Lindor KD, Kowdley KV, Harrison ME. ACG Clinical Guideline: Primary sclerosing cholangitis. *Am J Gastroenterol*. 2015;110:646–59.
4. Gudnason HO, Björnsson HK, Gardarsdottir M, et al. Secondary sclerosing cholangitis in patients with drug-induced liver injury. *Dig Liver Dis*. 2015;47(6):502–7.
5. Lemmer ER, Robson SC, Jaskiewicz K, Levitt C, Krige JE. Malignant obstructive cholangiopathies mimicking primary sclerosing cholangitis. *J Clin Gastroenterol*. 1994;19(1):86–8.
6. Gossard AA, Angulo P, Lindor KD. Secondary sclerosing cholangitis: A comparison to primary sclerosing cholangitis. *Am J Gastroenterol*. 2005;100:1330–3.
7. Taylor J, Lindor K. Metastatic prostate cancer simulating sclerosing cholangitis. *J Clin Gastroenterol*. 1993;16(2):143–5.
8. Fan DS, Sorser SA, Gamarra RM. Secondary sclerosing cholangitis due to gallbladder adenocarcinoma. *Case Rep Gastroenterol*. 2013;7(1):134–139.
9. Vilgrain V, Erlinger S, Belghiti J, Degott C, Menu Y, Nahum H. Cholangiographic appearance simulating sclerosing cholangitis in metastatic adenocarcinoma of the liver. *Gastroenterology*. 1990;99(3):850–3.
10. Poropat G, Giljaca V, Stimac D, Gluud C. Bile acids for primary sclerosing cholangitis. Cochrane Database Syst Rev. 2011;CD003626.
11. Brandt DJ, MacCarty RL, Charboneau JW, LaRusso NF, Wiesner RH, Ludwig J. Gallbladder disease in patients with primary sclerosing cholangitis. *AJR Am J Roentgenol*. 1988;150:571.
12. Burak KW, Angulo P, Lindor KD. Is there a role for liver biopsy in primary sclerosing cholangitis? *Am J Gastroenterol*. 2003;98:1155.
13. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo primary sclerosing cholangitis-ursodeoxycholic acid study group. *N Engl J Med*. 1997;336:691.
14. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375 (7):631–43.
15. Johnson GK, Geenen JE, Venu RP, Schmalz MJ, Hogan WJ. Endoscopic treatment of biliary tract strictures in sclerosing cholangitis: A larger series and recommendations for treatment. *Gastrointest Endosc*. 1991;37 (1):38–43.
16. Lee JG, Schutz SM, England RE, Leung JW, Cotton PB. Endoscopic therapy of sclerosing cholangitis. *Hepatology*. 1995;21(3):661–7.