Primary Sclerosing Cholangitis Complicating Ulcerative Colitis, Two Liver Transplants and Colorectal Carcinoma: A Case Report Spanning 25 Years

by Michelle Maciag, Osamuyimen Igbinosa

INTRODUCTION

A 55 year-old woman from Guyana presented to the Emergency Department with a two-day history of anorexia, diarrhea, nausea and non-bilious vomiting. Prior to this, she had noticed one month of abdominal bloating. She denied fever, urinary symptoms, significant abdominal pain, recent sick contacts or history of recent travel.

In 1981, at age 24, the patient developed loose bowel movements with progression to rectal bleeding. Colonoscopy with biopsies established the diagnosis of ulcerative colitis (UC). She was treated with sulfasalazine, but continued to have loose, bloody stools until mesalamine was prescribed.

Ten years later, at age 34, she presented to her gastroenterologist with extreme fatigue. On routine laboratory evaluation, elevations in her AST, ALT and alkaline phosphatase were noted, indicating a cholestatic pattern.

Question 1. Given a history of UC and the current symptom of fatigue, in the setting of a cholestatic biochemical profile, which one of the following would be the best initial study in obtaining her diagnosis?

a. Liver ultrasound only
b. Liver biopsy
c. MRCP (Magnetic Resonance Cholangiopancreatography)
d. ERCP (Endoscopic Retrograde Cholangiopancreatography)
e. IgG4 levels

Primary sclerosing cholangitis, or PSC, should always be considered in patients with inflammatory bowel disease who have elevated serum alkaline phosphatase. Most patients are asymptomatic at the time of diagnosis, but if symptomatic, they usually present with fatigue and pruritus. PSC complicates UC in 5% of patients. See Table 1 for the extra-intestinal manifestations of UC. Other diagnoses to be considered include primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH). Table 2 compares these hepatitides.

PSC can be diagnosed by MRCP demonstration of characteristic multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts. Although MRCP provides good image quality, it is only diagnostic for extrahepatic bile duct abnormalities. However, it may serve as an alternative to ERCP. Traditionally, ERCP has been regarded as the gold standard for diagnosing PSC as it better evaluates the intrahepatic ductal system. ERCP is usually unnecessary in a patient with a high pretest probability of having PSC because it is invasive and carries a higher risk of complications than MRCP. In a meta-analysis of six studies, MRCP was shown to have 84% sensitivity and 96% specificity in detecting PSC. Thus, in patients with a high pretest probability for PSC, MRCP may be confirmatory.

Liver ultrasound may suggest abnormal bile ducts but is not diagnostic.

Percutaneous liver biopsy may support the diagnosis of PSC, but is rarely diagnostic in early disease. The American Association for the Study of Liver Diseases (AASLD) recommends against routine liver biopsy for diagnosis of PSC in patients with the typical cholangiographic findings. The specific histologic finding of PSC is fibrous obliteration of small bile ducts, with concentric replacement by connective tissue, described by pathologists as “onion skin.”
This characteristic appearance initially involves only the portal triads, but later expands into the hepatic parenchyma, therefore, once it is diagnosed, biopsy may be helpful in staging the disease.

Diseases associated with increased immunoglobulin G4 (IgG4), like autoimmune pancreatitis and IgG4-associated cholangitis, are rare steroid-responsive disorders that share similar clinical and biochemical features with PSC. Since these disorders can be treated pharmacologically, the AASLD suggests that serum IgG4 be measured in all newly diagnosed patients with PSC to exclude these diseases.5

**Question 2. Which of the following management options is known to forestall disease progression in PSC?**

- a. Ursodeoxycholic acid
- b. Liver transplant
- c. Anti TNF agent
- d. Methotrexate

The two major goals of treatment in PSC are to 1) slow the progression of the disease process and 2) manage its complications. No treatment has been shown to alter the progression of PSC other than liver transplant. Outcomes for liver transplantation for this indication are equivalent to, or better than other indications for liver transplant.6,7 At age 38, the patient presented above received a transplant from a male cadaveric donor while her UC remained in clinical remission.

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, is thought to stimulate hepatobiliary secretion, and protect cholangiocytes against toxic bile acids that accumulate in the liver in cholestatic liver diseases. Meta-analysis shows that UDCA improves biochemical abnormalities and stabilizes hepatic inflammation in PSC, but does not increase survival or delay the need for liver transplant.8 Currently, the AASLD recommends against use of UDCA in the treatment of PSC based on lack of reproducible benefits regarding meaningful endpoints, namely death or liver transplantation. Additionally, it may be harmful at high doses. A study of 150 PSC patients on high doses of UDCA was prematurely halted due to the increased risk of death, liver transplant or serious adverse effect.5

Since tumor necrosis factor released from Kupffer cells induces liver injury, the use of anti-TNF agents seems logical, however studies have failed to demonstrate increased survival in those treated with methotrexate or anti-TNF agents.9 Pilot studies using etanercept and infliximab revealed that these are no more effective than placebo.9,10 A double-blind, randomized trial of treatment with oral methotrexate versus placebo demonstrated reduced alkaline phosphatase in the methotrexate-treated group, but no difference in the histology, degree of stricturing on ERCP or clinical

**Table 1. Extra-Intestinal Manifestations of UC**

| Ophthalmologic: Uveitis, episcleritis, conjunctivitis |
| Dermatologic: Erythema nodosum, pyoderma gangrenosum |
| Arthritis: Affects large, peripheral joints, typically migratory, and non-destructive |
| *Ankylosing Spondylitis: most cases HLA-B27 positive |
| *Primary Sclerosing Cholangitis |
| Respiratory Involvement: bronchial involvement, parenchymal involvement |
| Venous & Arterial Thromboembolism: most commonly in peripheral veins, see ineffective fibrinolysis |
| Anemia: anemia of chronic disease, iron-deficiency anemia |
| *Manifestations of UC which progress irrespective of UC disease activity |

Table 2. Salient Features of AIH, PBC, and PSC

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female : Male</strong></td>
<td>4:1</td>
<td>9:1</td>
<td>1:2</td>
</tr>
<tr>
<td><strong>Elevated Liver Test</strong></td>
<td>ALT, AST</td>
<td>AlkP, GGT</td>
<td>AlkP, GGT</td>
</tr>
<tr>
<td><strong>Serum Ig Elevation</strong></td>
<td>IgG</td>
<td>IgM</td>
<td>IgG, IgM</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>ANA, ASMA, LKM, SLA, p-ANCA</td>
<td>AMA, AMA-M2</td>
<td>p-ANCA</td>
</tr>
<tr>
<td><strong>HLA Association</strong></td>
<td>A3, B8, DR3, DR4</td>
<td>DR8</td>
<td>DR52</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Lymphoplasmacytic infiltrate, moderate/severe hepatitis initially surrounding the portal triad and then expanding into the lobule</td>
<td>Bile duct damage progressing to loss, lymphoid follicles, classically granulomas</td>
<td>Fibrosing bile duct lesion, described as “onion-skinning”</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>AIH score &gt;7.</td>
<td>AMA-M2, cholestatic serum enzyme pattern, compatible histology</td>
<td>Bile duct stenosis/dilatations (cholangiography), cholestatic serum enzyme pattern, inflammatory bowel disease, p-ANCA</td>
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</tbody>
</table>

- 1 point per autoantibody listed above, maximum of 2 points
- 1 point if IgG elevated, 2 if elevated more than 10%
- 1 point if liver histology compatible with AIH, 2 if typical of AIH
- 2 points for absence of viral hepatitis

**First-Line Pharmacotherapy**

|               | Corticosteroids & azathioprine | UDCA | UDCA |

**AIH**: Autoimmune Hepatitis, **PBC**: Primary Biliary Sclerosis, **PSC**: Primary Sclerosing Cholangitis, **ALT**: Alanine Aminotransferase, **AST**: Aspartate Aminotransferase, **AlkP**: Alkaline Phosphatase, **GGT**: Gamma Glutamyltransferase, **ANA**: anti-nuclear antibody, **ASMA**: anti-smooth muscle antibody, **LKM**: liver kidney microsomal antibody, **SLA**: soluble liver antigen, **p-ANCA**: perinuclear anti-neutrophil cytoplasmic antibodies, **AMA**: anti-mitochondrial antibodies, **UDCA**: Ursodeoxycholic Acid


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outcome when compared to the control.\textsuperscript{11}

Two years after the liver transplant, the patient presented with lethargy, pruritus and abdominal fullness. A metabolic panel showed an elevation in her liver enzymes, again in a cholestatic pattern. A subsequent cholangiogram confirmed that the PSC had returned.

**Question 3. What percentage of patients experience recurrence of PSC after liver transplantation?**

- a. \( \leq 5\% \)
- b. 10\%
- c. 20\%
- d. 40\%

PSC recurs post-transplantation in roughly 20\% of patients.\textsuperscript{12} The likelihood of PSC recurrence directly correlates with the amount of time post-transplant. In one study, recurrence of PSC at one, five and ten years was found to be two, 12 and 20 percent, respectively. However, only about one-third of the patients who again develop PSC post-transplant require repeat liver transplant.\textsuperscript{13}

**Question 4. Which of the following has been shown to be a risk factor associated with the recurrence of PSC post-transplant?**

- a. Uveitis
- b. Ankylosing Spondylitis
- c. Presence of an intact colon
- d. Treatment of UC with only mesalamine

An intact colon in the setting of UC is an independent risk factor for PSC recurrence after liver transplantation. Transplant from a non-age and sex-matched cadaveric donor transplant also increases the risk of PSC recurrence as does comorbid IBD.\textsuperscript{14} Uveitis and ankylosing spondylitis, both extra-colonic manifestations of UC, have not been shown to be associated with post-transplant recurrence of PSC. See Table 3 for a complete list of the risk factors for the recurrence of PSC in a patient post-transplant.

At age 42, four years after her first liver transplant, the patient procured another liver transplant, this time from a 41 year-old cadaveric female. To prevent rejection, the patient was maintained on 5 mg of prednisone and 2 mg tacrolimus daily. At her most recent office visit with her transplant team, around two months before she presented at our institution, the patient’s liver graft was assessed to have optimal function. She remained in relatively good health for more than a decade, until age 53, when she again noticed blood in her stools. For over twenty years, she had been maintained on mesalamine, which left her UC quiescent. A colonoscopy was performed, and high-grade dysplasia was noted in the ascending colon.

Colonoscopy with biopsy at regular intervals is indicated for patients with pancolitis either annually or biannually beginning after 8 years in patients with limited colitis. The risk of colorectal cancer (CRC) is increased based on the length of time the patient has been afflicted with UC and the anatomical extent of the patient’s colitis.\textsuperscript{15}

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**Table 3. Risk Factors for Recurrence of PSC Post-Transplant**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td><em>Age/sex mismatch of donor</em></td>
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<td>Male recipient</td>
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<tr>
<td><em>Coexistent IBD</em></td>
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<tr>
<td><em>Presence of intact colon</em></td>
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<tr>
<td>CMV infection</td>
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<tr>
<td>Recurrent acute cellular rejection</td>
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<tr>
<td>Steroid-resistant cellular rejection</td>
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<tr>
<td>Use of OKT-3</td>
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<tr>
<td>Cholangiocarinoma before transplantation</td>
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<tr>
<td>Long-term glucocorticoid use</td>
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<tr>
<td><em>Risk factors of the patient</em></td>
<td></td>
</tr>
</tbody>
</table>

Primary Sclerosing Cholangitis

Table 4. Indications for Colectomy in Ulcerative Colitis

| Massive hemorrhage                      |
| Colonic perforation                     |
| Unresolving toxic megacolon             |
| Dysplasia or carcinoma                  |
| Failure of all medical therapy          |

**Question 5. In addition to this patient’s 22-year history with UC, and the extent of her colitis, what is an independent risk factor for her development of CRC?**

a. Comorbid PSC
b. Sex
c. Treatment with mesalamine only
d. Cardiomyopathy

Awareness regarding PSC as an independent risk factor for CRC has been increasing. A study of 211 patients concluded that, at ten years, patients with PSC and IBD had a CRC rate of 14%, whereas in their counterparts with IBD but without PSC, this rate was only 2%. At the 20-year mark, patients with PSC and IBD had a CRC rate of 31%, while those with only IBD had a CRC rate of only 2%. Conclusively, a meta-analysis of 11 different studies has confirmed that the risk of developing CRC in patients with both UC and PSC is four times that of UC alone. Although CRC is the third most common cancer affecting both men and women, it is more common in males than females in both whites and blacks. Therefore, her female sex is not considered an independent risk factor for CRC.

One study hypothesizes that PSC increases the proportion of bile acids that are cytotoxic to the mucosal cells of the colon, like deoxycholic acid, and lithocolic acid. These mutagenic bile acids are present in lower concentrations in the colons of patients without PSC. These bile acids induce the aberrant replication of epithelial cells and cause neoplasia. Another hypothesis is that IBD associated with PSC induces a higher level of inflammation in the colon and is more mutagenic than IBD alone. This increased inflammation may precipitate the transformation from healthy mucosa to dysplasia.

**Question 6. What is the recommended frequency of screening colonoscopy for those with UC and PSC?**

a. Every six months
b. Every 1-2 years
c. Every 3 years
d. Eight years after diagnosis with UC

There is an increased risk for CRC in patients with UC and PSC. As of 2010, the AASLD recommends that those with both IBD and PSC undergo surveillance colonoscopy every one to two years after receiving the diagnosis of PSC. Biopsy samples should be taken. If available, flow cytometry should be employed to detect any aneuploid cells, which may indicate developing dysplasia.

As high-grade dysplasia had been found on colonoscopy, at age 54 the patient underwent the indicated total proctocolectomy. The indications for colectomy in UC are tabulated (Table 4). She was initially left with an ileal J-pouch anastomosis, and a diverting ileostomy to protect the anastomosis. Pathology of her colon showed chronic ulcerative pancolitis, and a highly dysplastic tubulovillous polyp in the ascending colon, amid a larger area of dysplasia. All fourteen excised lymph nodes were negative for tumor. A liver biopsy, taken intraoperatively, revealed nonspecific findings of sinusoidal dilatation, ductular reaction and portal fibrosis. Her ileostomy functioned well, and was reversed three months later.

After her colectomy, she noticed swelling in her abdomen. She was otherwise asymptomatic, and it was assumed that her ascites were as a result of retained fluid from her surgery. One month before presenting to our institution she consulted her gastroenterologist. He began a trial of furosemide to relieve the fluid accumulation. When this treatment failed to improve her symptoms, diagnostic paracentesis was performed, and a milky-white fluid was withdrawn. Further analysis of the fluid revealed that it had a triglyceride component of over 200 mg/dL, well above the 110 mg/dL cutoff necessary to diagnose chylous ascites.
Although chylous ascites was diagnosed, its etiology was unclear. See Table 5 for a differential diagnosis of chylous ascites.

Chylous ascites typically presents with painless abdominal distension, which may develop over months. Vague symptoms, like nausea, diarrhea, and abdominal pain are reported. A week after the paracentesis, the patient presented to our institution with these very symptoms—a two day history of nausea, vomiting and intractable diarrhea. On admission, her alkaline phosphatase was normal at 113 IU/L. AST was slightly elevated at 48 IU/L. Her ALT was normal, at 39 IU/L. Total protein and albumin were dramatically low at 4.2 g/dL and 2.2 g/dL respectively, indicating poor synthetic function of her liver.

Her worsening ascites post-colectomy makes a traumatic etiology for the chyle leak the most likely explanation. According to one study, chylous ascites after surgery for colorectal cancer occurred at an overall incidence of 1%. The incidence of chylous ascites is significantly higher after surgery for tumors fed by the superior mesenteric artery, as was the case in our patient, with her cancer involving the ascending colon. If colon supplied by this artery is resected, there was a 5.6% rate of chylous ascites. In cases of chylous ascites due to traumatic injury after resection of colon cancer, conservative management, especially limiting ingestion of high-fat foods, is effective. This was recommended to the patient, and she was then referred to the tertiary institution where her liver transplant and colectomy were done to reassess the function of her liver graft.

CONCLUSION

We have described a long-standing case of UC with an attempt to review all of its extracolonic manifestations as well as its current management guidelines. The patient described in this case had a difficult course highlighting many of the consequences associated with UC. In addition to her primary diagnosis, she suffered refractory PSC, a failed liver transplant and colorectal cancer. Finally, she was hospitalized with chylous ascites, likely secondary to a traumatic injury after surgery.

In any patient with ulcerative colitis, the goal of treatment is to suppress both colonic and extracolonic inflammatory symptoms. This is integral to slowing disease progression and limiting disease burden. As detailed above, long term screening for neoplastic, cholestatic and medical complications is strongly recommended for any patient with a diagnosis of UC. More prospective studies are needed to understand all of the implications of UC and how its management may be optimized, especially in the setting of comorbid PSC.

Special gratitude to CS Pitchumoni, MD, S Kastuar, MD, and the many other fine physicians involved in this patient’s care.

References

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A CASE REPORT

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Answers to this month’s crossword puzzle:

C I R R H O S I S  G E R D
O E O O C U E A
M U C O U S C C N O T C H
A T R E V E N E E R
T R A N S A C Y L A S E C
O I L S I R S B O
S B BRUGIA SUM O
E D I L L P D I P
F I L M F A P A N E T H
A P O D O R R I S O
N Y H A N R E S E R V O I R
O A T E P N I
D Y S P H A G I A J O I N T
A I L U S A D I
L C R Y P T M A R K E R S