# Leukocytapheresis Therapy Improved Cholestasis in a Patient Suffering from Primary Sclerosing Cholangitis with Ulcerative Colitis

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**Abstract**

Primary sclerosing cholangitis (PSC) is an autoimmune disease of the hepatobiliary system for which effective therapy has not been established. Leukocytapheresis (LCAP) therapy is known to effective in patients with ulcerative colitis (UC). In addition, effects of LCAP therapy were reported on some autoimmune diseases such as Crohn's disease, rheumatoid arthritis and rapidly progressive glomerulonephritis. Here we report the case of a 29-year-old man with PSC associated with UC who was treated with LCAP therapy. He had a 16-year history of UC and a 12-year history of PSC. Although he was under treatment with prednisolone and ursodeoxycholic acid, exacerbation of UC and PSC-associated cholestasis were seen. Since he showed side effects of prednisolone, he was treated with LCAP. Not only improvement of UC, but also decreased serum alkaline phosphatase, γ-guanosine triphosphate and total bile acids, suggesting improvement of PSC-associated cholestaisis, were seen after treatment with LCAP. Our experience with this case suggests that LCAP therapy could be a new effective therapeutic strategy for patients with PSC associated with UC.

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## Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of unknown etiology. It is characterized by inflammation and fibrosis of the biliary tree, with eventual liver cirrhosis and a high risk of cholangiocarcinoma. PSC may occur in the presence or absence of inflammatory bowel disease. The prevalence of inflammatory bowel disease (typically ulcerative colitis, UC) among PSC patients is approximately 70–80%, whereas only 2–7.5% of patients with UC will develop PSC [1]. Although therapeutic trials of ursodeoxycholic acid, D-penicillamine, tacrolimus, corticosteroids, azathioprine [2], methotrexate and bezafibrate have been conducted [1], effective medical therapy has not been shown to alter the progressive course of PSC. While liver transplantation is regarded as the only life-extending therapeutic alternative for patients with PSC, the disease has also been known to recur after transplantation [3, 4].

Recently, leukocytapheresis (LCAP) therapy has been shown to improve the exacerbation of UC. The effectiveness of LCAP on Crohn's disease, rheumatoid arthritis, and rapidly progressive glomerulonephritis is also reported [5]. Furthermore, it is reported that LCAP is effective for extraintestinal complications of inflammatory bowel disease, including pyoderma gangrenosum [6] and aortitis syndrome [7]. However, there are as yet no reports on the efficacy of LCAP for PSC associated with UC. Here, we report the first patient with PSC in whom LCAP improved cholestasis.

## Case Report

A 29-year-old male was under regular treatment at the outpatient department of our hospital for UC with PSC. The patient, who suffered from abdominal pain and bloody mucus diarrhea since he was 10 years of age, was diagnosed by colonoscopy to have active UC, and treatment with prednisolone was initiated. At age 14, laboratory tests showed mild abnormalities of liver function parameters, with elevated serum levels of biliary enzymes, including alkaline phosphatase (ALP) and γ-guanosine triphosphate (γ-GTP). Abdominal ultrasonography and computed tomography revealed multiple strictures and dilatation of the intra- and extrahepatic bile ducts. Endoscopic retrograde cholangiopancreatography showed pathognomonic strictures of the intra- and extrahepatic bile ducts, giving a 'beads-on-a-string' appearance (**fig. 1**a). Diagnostic imaging such as abdominal ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography, magnetic resonance imaging and magnetic resonance cholangiopancreatography showed no malignancy of the bile duct. In addition, stone disease, bacterial infection, pancreatitis, or surgical/procedural trauma was not seen. Furthermore, laboratory data showed negative results of various autoantibodies such as antimitochondrial antibody, antinuclear antibody, and myeloperoxidase antineutrophil cytoplasmic antibody. The specimen of liver biopsy showed concentric layers of fibrotic tissue surrounding the bile duct lesions, the bile duct at the center was infiltrated with neutrophils and lymphocytes and epithelial cells were damaged. Proliferation of the bile ducts were also seen (fig. 1b) [8, 9]. We diagnosed this case as PSC associated with UC by the criteria of the Mayo clinic [9]. Treatment with ursodeoxycholic acid was initiated, and subsequently the patient was followed up at our hospital with occasional relapses of UC and gradual worsening of PSC.

At age 29, the patient began to complain again of abdominal pain and bloody mucus diarrhea. Although treatment with ursodeoxycholic acid at a dose of 600 mg/day and prednisolone at a dose of 5 mg/day was continued, no improvement was noted. Colonoscopy was performed, which revealed evidence of active UC with diffuse mucosal inflammation and ulcerations in the left-sided colon. Simultaneously, laboratory tests showed elevated serum levels of biliary enzymes, including ALP and γ-GTP, and of total bile acid and total bilirubin levels, indicating exacerbation of the PSC (**table 1**). Magnetic resonance cholangiopancreatography showed a typical 'beads-on-a-string' appearance (**fig. 2**) and there were no findings suggesting malignancy, stone or secondary cholangitis. Neither were pathogenic bacteria detected in feces cultivation. The patient had been treated with a total of more than 20 g of prednisolone since he was diagnosed with UC. In order to avoid the occurrence of side effects, he was not likely to tolerate additional steroid therapy. In fact, his mineral quantitation by digital image processing indicated osteoporosis, and oral candidiasis was seen. Under these circumstances, LCAP

therapy was initiated with once-a-week sessions for five weeks. LCAP was performed using a Cellsorba E column (Asahi Medical, Tokyo, Japan) installed in the extracorporeal circulation system (Plasauto LC, Asahi Medical) [10]. For apheresis, venous access was secured via two large peripheral veins, and the blood was anticoagulated with nafamostat mesilate (Torii Pharmaceutical, Tokyo, Japan), a protease inhibitor that inhibits the activity of coagulation factors and platelet aggregation. With a flow rate of 30–50 ml/min for 60 min, a total of approximately 2.5 l of blood was treated during each session. Previous data show that nearly 100% of neutrophils and monocytes that entered the filter, and 40–60% of lymphocytes were removed in one session of LCAP [11]. Marked improvement of both the clinical symptoms and colonoscopic findings of UC were noted in response to LCAP therapy. Serum levels of ALP, total bile acids and total bilirubin were decreased (fig. 3). Follow-up of the patient revealed no exacerbation of disease activity for either UC or PSC for more than one year.

### Discussion

We experienced a patient with UC complicated by PSC who underwent LCAP and showed improvement not only in clinical signs and colonoscopic findings of UC, but also in PSC-associated cholestasis. The patient has been treated with a total of more than 20 g of prednisolone since he was diagnosed with UC. In order to avoid occurrence of side effects, he was not likely to tolerate additional steroid therapy. In fact, his mineral quantitation by digital image processing indicated osteoporosis, and oral candidiasis was seen. Therefore, we selected LCAP therapy.

There are at least two possible mechanisms underlying the improvement of PSC associated in this patient. One possibility is that the PSC may have improved via a mechanism similar to that underlying the improvement of UC [1]. As to the mechanism underlying the action of LCAP in UC, previous reports have described beneficial effects including suppression of proinflammatory cytokine release from leukocytes [12] and induction of bone marrow cells to repair the impaired intestine. Similar effects may also have been exerted in the impaired bile tract. The other possibility is that improvement of PSC may have been secondary to improvement of UC [13]. Some reports have shown that the impairment of intestinal mucosal integrity observed in UC may lead to the passage of luminal antigens into the portal vein, thereby leading to the development of PSC [14]. According to this possibility, treatment of UC by LCAP may improve PSC. However, we have to be cautious with the interpretation of cholestasis improvement. In previous reports, the improvement of PSC was evaluated using laboratory data: ALP, aspartate aminotransferase, total bilirubin and albumin [15]. However, the definition of improvement in PSC should not solely rely on laboratory data. In this case, there was no significant change in organic stricture of the bile duct after LCAP therapy. Although minimal improvement in bile the ducts may occur with LCAP therapy, we cannot deny the possibility of an effect due to the improvement of UC.

In conclusion, we conducted LCAP in a patient with PSC associated with UC. He showed improvement not only in UC, but also in PSC. No effective therapy for PSC is known at present. Improvement of PSC-associated cholestasis was seen in this case. Therefore LCAP may be a new effective therapeutic strategy for PSC associated with UC.

**Table 1.** Laboratory data at relapse of UC

| | | | |
|---|---|---|---|
| WBC | 9,000 /ml | ALT | 44 U/l |
| RBC | 547 ×10³/ml | LDH | 144 U/l |
| Hb | 11.8 g/100 ml | ALP | 553 U/l |
| HCT | 38.7% | γ-GTP | 98 U/l |
| MCV | 70.7 fl | TB | 0.7 mg/100 ml |
| MCH | 21.6 pg | DB | 0.09 mg/100 ml |
| MCHC | 30.5 g/100 ml | TBA | 114.4 μmol/l |
| PLT | 42.9 × 10³/ml | TP | 7.54 g/100 ml |
| PT | 82% | ALB | 4.06 g/100 ml |
| CRP | 0.23 mg/100 ml | TTT | 16.7 U/l |
| HBs-Ag | Negative | ZTT | 17 U/l |
| HCV-Ab | Negative | BUN | 8.3 mg/100 ml |
| HIV-Ab | Negative | Cr | 0.76 mg/100 ml |
| ANA | Negative | Na | 140 mEq/l |
| AMA | Negative | K | 4.1 mEq/l |
| MPO-ANCA | Negative | Cl | 106 mEq/l |
| AST | 30 U/l | | |

WBC = White blood cells; RBC = red blood cells; Hb = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; PLT = platelet count; PT = prothrombin time; CRP = C-reactive protein; HBs-Ag = hepatitis B surface antigen; HCV-Ab = hepatitis C virus antibody; HIV-Ab = human immunodeficiency virus antibody; ANA = antinuclear antibody; AMA = antimitochondrial antibody; MPO-ANCA = myeloperoxidase antineutrophil cytoplasmic antibody; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; ALP = alkaline phosphatase, lactic dehydrogenase; γ-GTP = γ-guanosine triphosphate; TB = total bilirubin; DB = direct bilirubin; TBA = total bile acids; TP = total protein; ALB = serum albumin; TTT = thymol turbidity test; ZTT = zinc sulfate turbidity test; BUN = blood urea nitrogen; Cr = creatinine; Na = sodium ion; K = potassium ion; Cl = chloride.

**Fig. 1. a** Endoscopic retrograde cholangiopancreatography shows pathognomonic stricture of intra- and extrahepatic bile ducts and 'beads-on-a-string' appearance. **b** Liver biopsy shows concentric layers of fibrotic tissue surrounding the bile duct lesions (arrow); the bile duct at the center is infiltrated with neutrophils and lymphocytes and epithelial cells are damaged. Proliferation of the bile ducts is also seen.
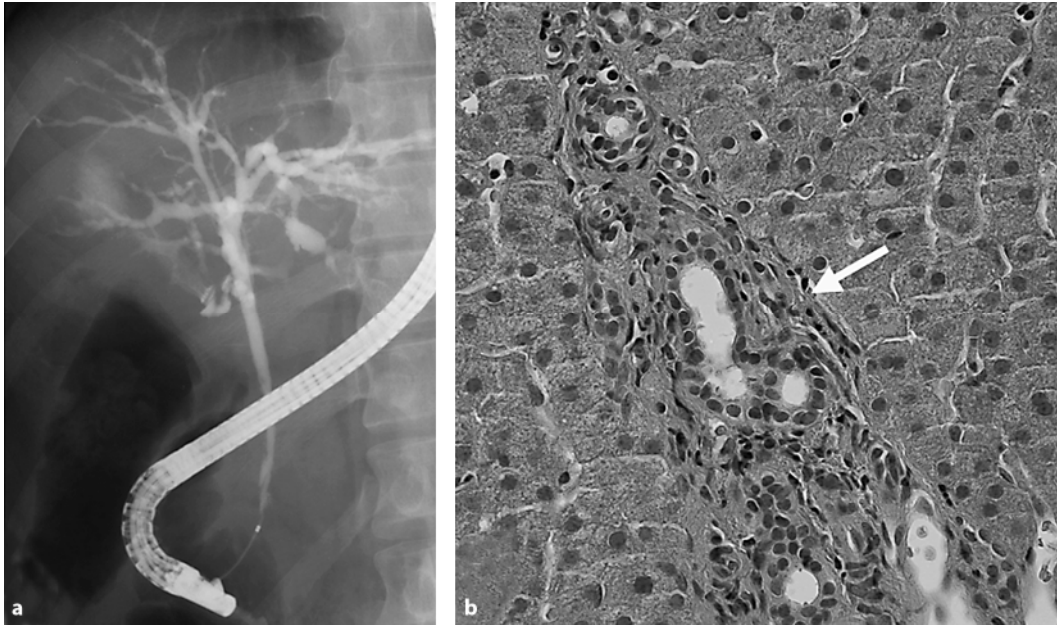


**Fig. 2.** Magnetic resonance cholangiopancreatography shows pathognomonic stricture of the intra- and extrahepatic bile ducts and no malignancy or cholecystolithiasis.
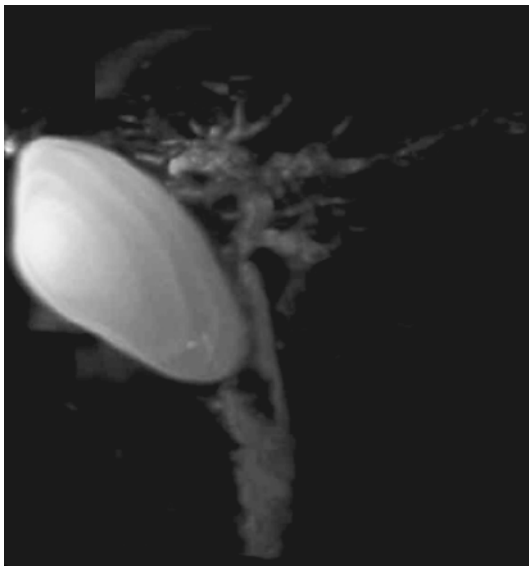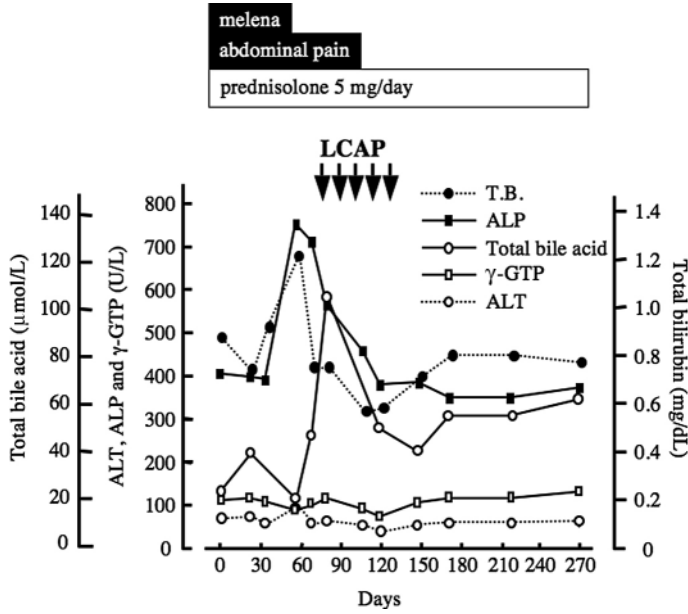
**Fig. 3.** The effect of LCAP on exacerbation of PSC-associated cholestasis. Exacerbation of PSC-associated cholestasis occurred after relapse of UC. Abnormality in serum ALP, γ-GTP, total bilirubin and total bile acids gradually decreased over the course of five LCAP procedures.

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