

A Case of Primary Biliary Cirrhosis That Progressed Rapidly after Treatment Involving Rituximab

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Key Words

Primary biliary cirrhosis · Rituximab · Transforming growth factor beta

Abstract

Primary biliary cirrhosis (PBC) is a progressive liver disease for which limited therapies are recommended. Rituximab, an anti-CD20 monoclonal antibody, is expected to be a useful therapeutic regimen for PBC. Previous studies indicated biochemical and immunological improvement in PBC after rituximab treatment. Although rituximab shows therapeutic potential for PBC, few cases have been reported and histological improvement and long-term outcome remain uncertain. Here, we report a case of PBC in a 66-year-old Japanese female patient who presented with a gastric lymphoma and who had been treated with a regimen containing rituximab for incidental malignant lymphoma. She showed biochemical and immunological improvements, and liver histology before and after rituximab treatment confirmed a decrease in liver inflammation. However, she developed liver cirrhosis a short time after rituximab treatment without biochemical or immunological worsening. Rituximab treatment for PBC might be considered and careful observation is required after treatment.

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease found predominantly in middle-aged women [1]. Although the precise pathogenesis of PBC is unclear, both B-cell and T-cell responses to the E2 subunit of the inner mitochondrial membrane pyruvate dehydrogenase complex (PDC-E2) have been implicated in its pathogenesis [2, 3]. Indeed,

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anti-mitochondrial antibody (AMA), particularly directed toward PDC-E2, is found in most patients with PBC and has a significant value in diagnosis [1]. Ursodeoxycholic acid is the only recommended therapy for patients with PBC with regard to longer survival [4]. Several clinical trials with immunosuppressants, such as corticosteroids or mycophenolate mofetil, failed to show clinical benefits [5–7]. Liver transplantation is the only recommended therapy for patients with progressed PBC [4].

Recently, a role for rituximab, a monoclonal antibody against human CD20, has been suggested in the treatment for PBC [8]; treatment with rituximab was reported to reduce the levels of serum alkaline phosphatase (ALP), serum IgM and AMA, suggesting that rituximab may be effective in the therapy of PBC. Here, we report a female patient with PBC treated with rituximab for incidental malignant lymphoma. After rituximab treatment, she showed improvement of serum biliary enzyme, serum IgM level, AMA titer and hepatic histological inflammation. However, she developed liver cirrhosis within a short time after the treatment.

Case Report

A 66-year-old woman was referred to our hospital for treatment of a gastric tumor. She had been diagnosed with PBC at the age of 60 years and had been treated with ursodeoxycholic acid. Although she had been stable and asymptomatic for several years, a gastric tumor was detected on upper gastric endoscopy performed due to abdominal discomfort after meals a month before visiting a local hospital. Abdominal computed tomography (CT) and 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) showed the localized stage of malignant lymphoma in her stomach. Endoscopic biopsy examination confirmed diffuse large B-cell lymphoma (DLBCL). She showed good performance status (PS1) and normal serum lactate dehydrogenase level (189 IU/l, normal range 121–220 IU/l). She had been diagnosed with gastric DLBCL with stage II₁ in the Lugano classification and showed low international prognostic index (IPI, 1 point) [9]. With regard to PBC status, she had no jaundice (serum total bilirubin 1.0 mg/dl, normal range 0.2–1.3 mg/dl) and showed well-preserved liver function (serum albumin 4.0 g/dl, normal range 4.0–5.0 g/dl; PT% 100%, normal range 80–120%), although biliary enzyme levels were slightly elevated (gamma-glutamyl transpeptidase 214 U/l, normal range 10–47 U/l; ALP 826 U/l, normal range 115–359 U/l). Her serum IgM and AMA-M2 titers were high (IgM 615 mg/dl, normal range 57–288 mg/dl; AMA-M2 70, normal index <7), reflecting PBC.

Prior to treatment for DLBCL, we performed a biopsy on the right lobe of the liver and found chronic non-suppurative destructive cholangitis with interface hepatitis consistent with PBC at Scheuer's histological stage II (fig. 1a, b). According to the risk score of PBC, her risk score before treatment of DLBCL was calculated as 5.5 and the estimated probability of survival for 24 months was >99% [10]. Thereafter, she was treated with chemotherapy, including rituximab (R-CHOP – cyclophosphamide/hydroxydaunorubicin/ondovon/prednisone, rituximab 375 mg/m²) plus radiation 40 Gy as shown in figure 2. After treatment with 8 doses of rituximab, her biliary enzyme and serum IgM levels decreased gradually and the AMA titer also decreased (fig. 2). Moreover, we found that portal inflammation had decreased after rituximab treatment (fig. 1c, d). She finished R-CHOP plus radiation therapy and achieved complete remission of DLBCL. Thereafter, she was observed and remained in a stable condition for 24 months after diagnosis of DLBCL. She was asymptomatic and her PBC Mayo risk scores remained low for 24 months after diagnosis of DLBCL (fig. 2). However, she showed marked jaundice and ascites without elevation of serum AMA titer 30 months after

diagnosis of DLBCL. CT scan showed bile duct cancer at the bottom of the common bile duct in addition to cirrhotic changes such as ascites. Percutaneous drainage of the bile duct was immediately and successfully performed and her jaundice was partially decreased, but surgical resection or chemotherapy could not be done due to decreased liver function. Hepatobiliary scintigraphy using ^{99m}Tc -PMT showed disturbance of hepatocellular excretion of bile (data not shown). Therefore, her cirrhosis was estimated to be already established at the time when jaundice developed. She received the best supportive care and died from liver failure 3 years after diagnosis of DLBCL. Autopsy showed bridged fibrosis formation of the liver (fig. 3a, b, Scheuer's histological stage IV) and lower bile duct cancer. Prominent infiltration of inflammatory cells was not found in the liver (fig. 3c).

Discussion

PBC is a chronic cholestatic liver disease predominant in middle-aged women, and no recommended therapy other than ursodeoxycholic acid has been reported [4]. Recently, the anti-CD20 monoclonal antibody rituximab was suggested as a treatment option for PBC [8, 11]. Biological and immunological improvements, such as of biliary enzyme, serum IgM and serum AMA titer, have been reported [8, 11]. However, histological improvement has not been reported previously. In addition to biological and immunological improvements in the case presented here, histological inflammation was also improved after rituximab treatment. Our results demonstrated the histological effectiveness of rituximab for liver inflammation and may support the effectiveness of rituximab as a treatment option for PBC.

However, our case showed rapid progression to cirrhosis within a short time without remarkable elevation of biliary enzymes or AMA titer (fig. 2). The Mayo risk scores of our case had remained relatively low until 24 months after diagnosis of DLBCL. The cirrhosis in this case was therefore estimated to have been established within a short time. Several mechanisms of rapid fibrosis progression might be considered. First, the controversial effect of rituximab should be discussed. In previous studies in animal models, B-cell depletion with anti-CD20 antibody had been shown to exacerbate cholangitis, and the authors recommended care regarding application of anti-CD20 antibody therapy against PBC in humans [12]. In a previous human study of rituximab, serum IgM or inflammatory cytokine seemed to be increased in a proportion of cases [8]. Serum IgM was also increased transiently in our case, suggesting a conflicting effect of cessation of rituximab treatment. In addition, the elevation of transforming growth factor beta (TGF- β) mRNA in CD4+ T-cells after treatment of PBC was reported [8]. TGF- β is known as a fibrogenic factor [13]. Although TGF- β was not evaluated in the present case, careful observation might be considered after treatment with rituximab for PBC. Second, the patient had been treated with CHOP and radiation in addition to rituximab. CHOP and radiation therapy may induce fibrosis at the site of radiation. However, the site of radiation in our case was the stomach, which was different and distant from the liver. In the present case, there were no increases in biliary enzyme levels during either CHOP or radiation therapy, and the time after CHOP and radiation therapy was relatively short (fig. 2). Thus, it seems unlikely that the observed effects were due to CHOP and radiation. Third, the possibility that obstructive jaundice due to bile duct cancer induced fibrosis of the liver should be discussed. Bile duct obstruction is known to induce liver fibrosis [14]. However, successful bile duct drainage had been performed in our case. In our case, hepatobiliary scintigraphy using ^{99m}Tc -PMT suggested disturbance of hepatocellular excretion of bile rather than obstruction of the lower bile duct. Furthermore, cirrhotic changes such as ascites or hypoalbuminemia had already been found when her bile duct cancer had

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been detected first. Her cirrhosis was thought to be established when bile duct cancer was found. Thus, obstructive jaundice is unlikely to have been the main cause of cirrhosis.

Conclusion

We reported a case of PBC rapidly progressing to cirrhosis after rituximab treatment. Bile duct inflammation improved biochemically, immunologically and histologically after rituximab treatment, suggesting that rituximab may be a useful treatment option for PBC. As the precise mechanism of fibrosis progression in our case remained unclear, careful observation is required after the administration of rituximab for treatment of PBC.

References

- 1 Kaplan MM, Gershwin ME: Primary biliary cirrhosis. *N Engl J Med* 2005;353:1261–1273.
- 2 Gershwin ME, Mackay IR, Sturgess A, Coppel RL: Identification and specificity of a cDNA encoding the 70 kd mitochondrial antigen recognized in primary biliary cirrhosis. *J Immunol* 1987;138:3525–3531.
- 3 Kita H, Matsumura S, He XS, Ansari AA, Lian ZX, Van de Water J, Coppel RL, Kaplan MM, Gershwin ME: Quantitative and functional analysis of PDC-E2-specific autoreactive cytotoxic T lymphocytes in primary biliary cirrhosis. *J Clin Invest* 2002;109:1231–1240.
- 4 Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ: Primary biliary cirrhosis. *Hepatology* 2009;50:291–308.
- 5 Mitchison HC, Palmer JM, Bassendine MF, Watson AJ, Record CO, James OF: A controlled trial of prednisolone treatment in primary biliary cirrhosis. Three-year results. *J Hepatol* 1992;15:336–344.
- 6 Angulo P, Jorgensen RA, Keach JC, Dickson ER, Smith C, Lindor KD: Oral budesonide in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. *Hepatology* 2000;31:318–323.
- 7 Treiber G, Malfertheiner P: Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2005;39:837–838; author reply 838.
- 8 Tsuda M, Moritoki Y, Lian ZX, Zhang W, Yoshida K, Wakabayashi K, Yang GX, Nakatani T, Vierling J, Lindor K, et al: Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Hepatology* 2012;55:512–521.
- 9 Cortelazzo S, Rossi A, Roggero F, Oldani E, Zucca E, Tondini C, Ambrosetti A, Pasini F, Pinotti G, Bertini M, et al: Stage-modified international prognostic index effectively predicts clinical outcome of localized primary gastric diffuse large B-cell lymphoma. International Extranodal Lymphoma Study Group (IELSG). *Ann Oncol* 1999;10:1433–1440.
- 10 Murtaugh PA, Dickson ER, Van Dam GM, Malinchoc M, Grambsch PM, Langworthy AL, Gips CH: Primary biliary cirrhosis: prediction of short-term survival based on repeated patient visits. *Hepatology* 1994;20 (1 Pt 1):126–134.
- 11 Polido-Pereira J, Rodrigues AM, Canhao H, Saraiva F, da Silva JA, Fonseca JE: Primary biliary cirrhosis in a rheumatoid arthritis patient treated with rituximab, a case-based review. *Clin Rheumatol* 2012;31:385–389.
- 12 Dhirapong A, Lleo A, Yang GX, Tsuneyama K, Dunn R, Kehry M, Packard TA, Cambier JC, Liu FT, Lindor K, et al: B cell depletion therapy exacerbates murine primary biliary cirrhosis. *Hepatology* 2011;53:527–535.
- 13 Dooley S, ten Dijke P: TGF- β in progression of liver disease. *Cell Tissue Res* 2012;347:245–256.
- 14 Glaser SS, Gaudio E, Miller T, Alvaro D, Alpini G: Cholangiocyte proliferation and liver fibrosis. *Expert Rev Mol Med* 2009;11:e7.

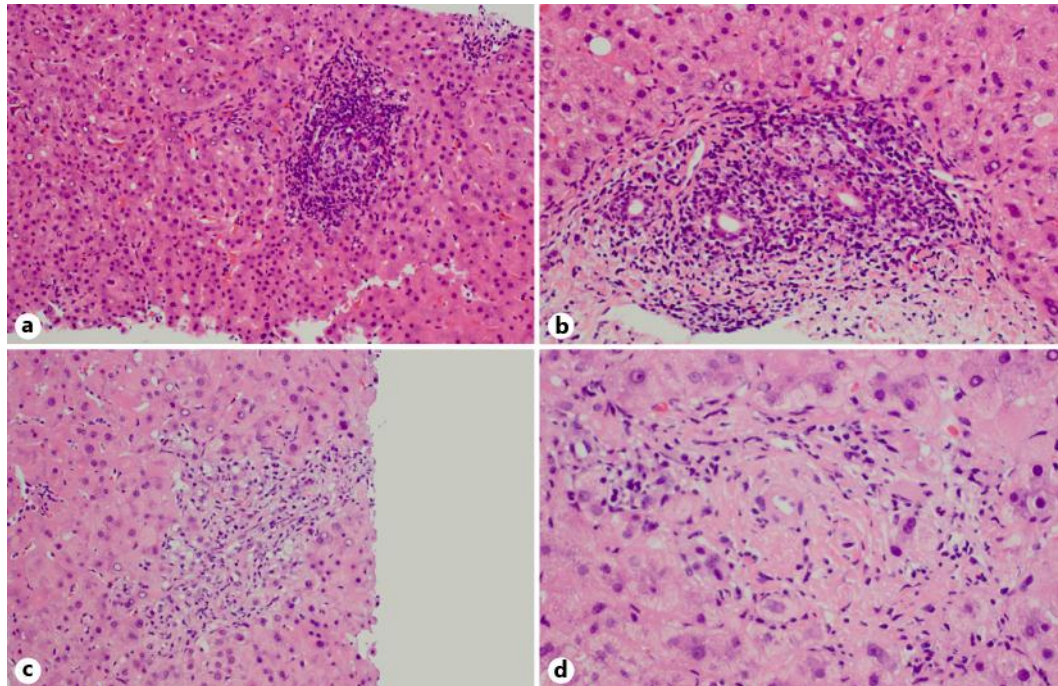


Fig. 1. Liver biopsy before and after rituximab treatment. H&E staining. **a, b** Before rituximab. Moderate lymphocyte and plasmacyte infiltration as well as chronic non-suppurative destructive cholangitis were found. Mild pericellular fibrosis was seen, but bridging fibrosis was absent. **a** $\times 40$; **b** $\times 400$. **c, d** After rituximab treatment, intralobular bile duct loss with minimal portal inflammation was seen. **c** $\times 40$; **d** $\times 400$.

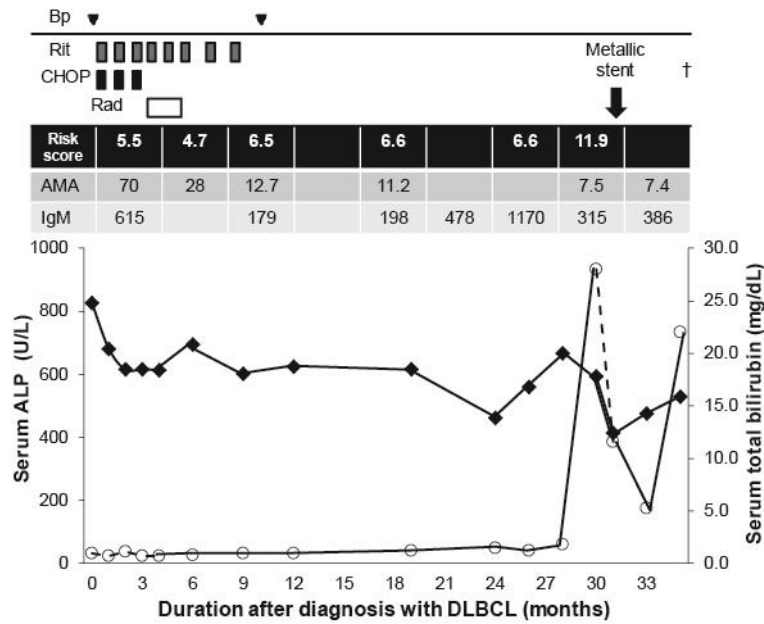


Fig. 2. Clinical course of this case. The arrowhead indicates the timing of liver biopsy (Bp). Gray bars indicate administration of rituximab (Rit), black bars indicate a cycle of CHOP. White bars indicate radiation (Rad). The Mayo risk score is shown (Risk score). The titers of AMA-M2 and IgM are shown. In the lower graph, the black square line indicates serum ALP level, whereas the circle dotted line indicates serum bilirubin level.

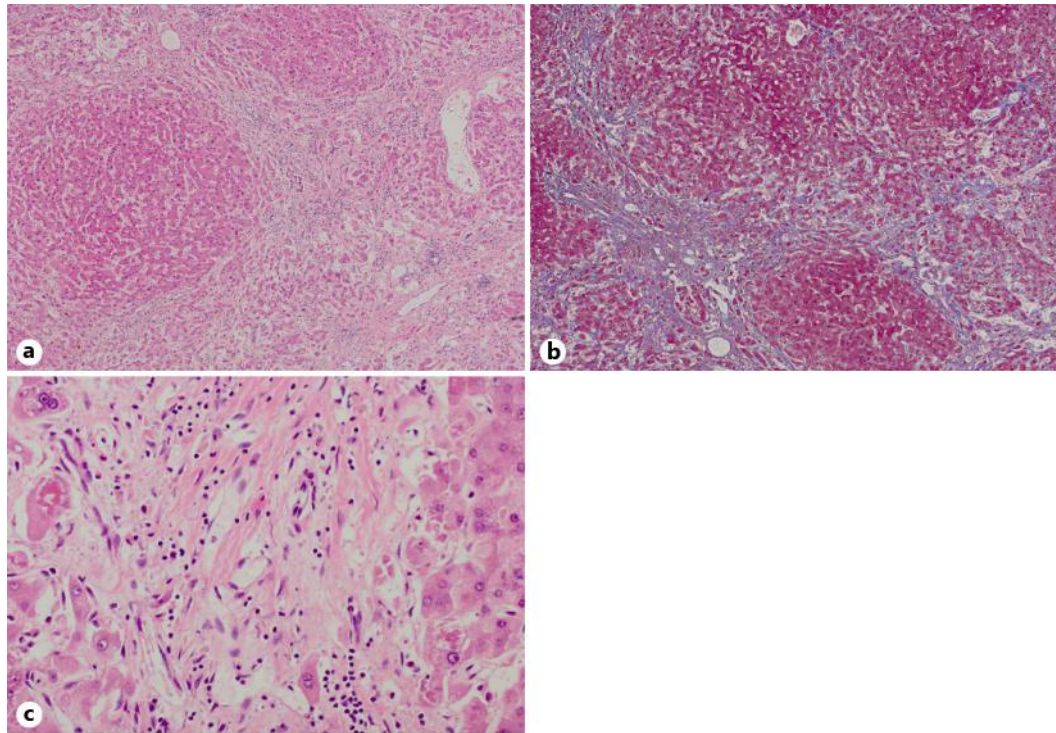


Fig. 3. Autopsy findings. **a, c** H&E staining; **b** Azan staining. **a, b** Bridging fibrosis was found ($\times 4$). **c** Portal inflammation was unclear ($\times 400$).