LETTER TO THE EDITOR

Pure red cell aplasia associated with concomitant use of mycophenolate mofetil and ribavirin in post-transplant recurrent hepatitis C

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Mycophenolate mofetil (MMF) is now widely used as an effective immunosuppressant especially in improving calcineurin inhibitors-induced nephrotoxicity [1]. In liver transplant (LT), combination therapy with interferon plus ribavirin is a promising post-transplantation antiviral therapy for recurrent hepatitis C [2,3]. We described here MMF and ribavirin developing pure red cell aplasia (PRCA) in a combined manner.

A 51-year-old man with decompensated liver cirrhosis had received LT. One year after LT, interferon α-2b and ribavirin were started to treat recurrent hepatitis C. Approximately, 2 weeks after the therapy commencement, normochromic and normocytic anemia occurred. PRCA was diagnosed by bone marrow biopsy revealing selective aplasia of erythroid progenitor cells, and ruling out other causes of anemia. The anemia did not improve despite discontinuing interferon/ribavirin. The MMF was then withdrawn, and the patient recovered rapidly (Fig. 1). Mycophenolate mofetil was restarted subsequently with the patient's approval because of rejection, and hemoglobin was stable around 12 g/dl for next 6 months. Then, we began interferon/ribavirin therapy again because of hepatitis C, and MMF was discontinued before restarting therapy to avoid myelosuppression. The interferon/ribavirin was continued for half-year, at which time hemoglobin was 10.8 g/dl.

Acquired PRCA is a rare hematological disease [4], and a number of causes have been described [5]. After exclusion of other causes, we made a diagnosis of drug-induced PRCA. The drugs that could be responsible for PRCA were MMF, tacrolimus, ribavirin, and interferon [6–10]. As demonstrated in Fig. 1, MMF plus interferon/ribavirin was supposed to relate to PRCA. Furthermore, interferon is eliminated rapidly because its half-life is about 5 h. Conversely, ribavirin has a multiple half-life of 12 days [11], and it may persist for several months. His actual ribavirin concentration was still 547 ng/ml at 4 weeks after discontinuing ribavirin on first administration. Therefore, the patient's clinical course suggested that co-administration of MMF and ribavirin was required for erythroid suppression (Fig. 1).

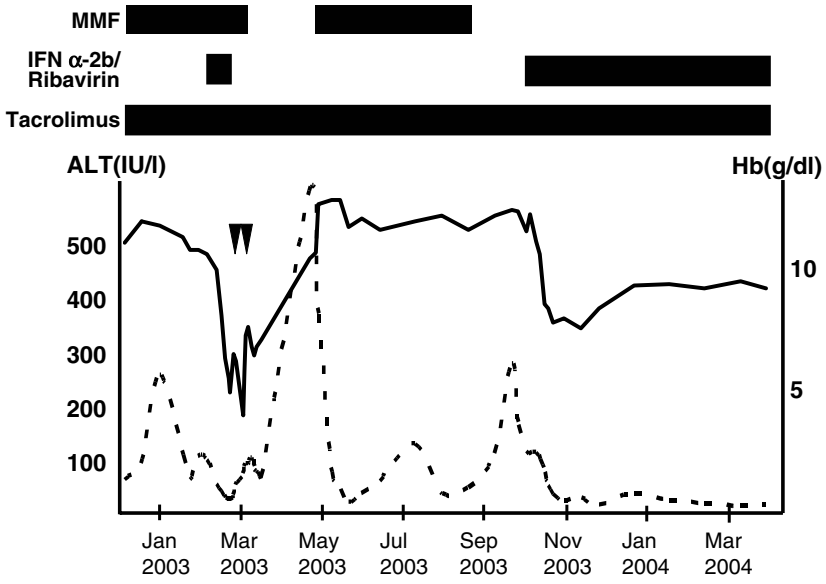

Figure 1 Changes in hemoglobin (Hb; solid line) and alanine aminotransferase (ALT; dotted line) level. Bars represent therapy of mycophenolat-mofetil (MMF), interferon α 2b (IFNα2b) and ribavirin. Each arrowhead indicates red blood cell transfusion. Concomitant administration of MMF and ribavirin caused red cell aplasia.

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), a noncompetitive inhibitor of inosine 5′-monophosphate dehydrogenase (IMPDH). Mycophenolic acid depletes the pool of dGTP required for *de novo* purine biosynthesis and has a cytostatic effect against activated lymphocytes, while other cells including erythropoietic precursors synthesize purines through the salvage pathway [12]. However, myelosuppression has been reported in renal transplant patients using MMF [13], and five cases of aplastic anemia have been reported to date [6,7]. These authors argued that stimulated stem cells with high turnover might switch purine synthesis pathways. On the other hand, ribavirin is a purine nucleotide analog with antiviral and immunological mechanisms. After intracellular transport, ribavirin is phosphorylated to monophosphate and competitively inhibits IMPDH [14]. Either MMF or ribavirin inhibits IMPDH, but they have diverse mechanisms of action. Thus, the antiproliferative effect was suggested to be because of a combined effect.

In summary, we describe PRCA caused by concomitant usage of MMF and ribavirin in the treatment of recurrent hepatitis C. Liver cirrhosis C has emerged as a leading indication of LT worldwide, and post-transplant hepatitis followed by graft loss and patient death is a universal problem [2]. However, the finding reported here indicates that caution is warranted in the use of ribavirin, especially in patients treated with MMF. This has significant implications for the concurrent antiviral and immunosuppressive treatment of hepatitis C.

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