Double Filtration Plasmapheresis in a Patient with Autoimmune Hepatitis-Systemic Lupus Erythematosus Overlap

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Double filtration plasmapheresis (DFPP) therapy was administered to a patient with autoimmune hepatitis (AIH)-systemic lupus erythematosus overlap. The patient had suffered from recurrent AIH attacks with an interval of 3-4 months despite massive corticosteroid administration. After vigorous removal of immunoglobulins by DFPP procedures combined with immunosuppressive therapies, clinical and laboratory findings of AIH were remarkably improved. DFPP might be an optional modality in the treatment of AIH patients, especially for those who are resistant to and/or cannot tolerate massive corticosteroid or immunosuppressive therapies.

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Introduction

Autoimmune hepatitis (AIH) is a liver disease characterized by hypergammaglobulinemia, diffuse intrahepatic lymphocyte infiltration, and the presence of various organ-specific and nonorgan-specific autoantibodies (1, 2). Although several liver-specific autoantibodies, such as anti-intracytoplasmic antigen(s) and anti-liver membrane antigen(s) have been identified (3, 4), the pathogenic role of increased gammaglobulin has not been fully recognized.

Double filtration plasmapheresis (DFPP), developed by Agishi et al (5), uses a 2 filter-system to semi-selectively remove large molecules, e.g., immunoglobulins, immune complexes and/or low density lipoproteins, from the patient’s plasma; the first filter is a plasma separator and the second removes pathogenic large molecules from the plasma.

We describe here an AIH patient complicated with systemic lupus erythematosus, whose condition could be controlled after the application of DFPP therapy.

Methods

To accomplish double filtration plasmapheresis (DFPP), plasma was separated from heparinized venous blood by polyethylene hollow fibers (OP-08, Asahi Medical, Tokyo) and subsequently introduced into a cellulose diacetate second filter (AC-1730, Asahi Medical). According to in vitro experiments, the second filter (mean pore size, 200 Å), is calculated to remove 40% of Dextran with a molecular weight of 100,000 Dalton, and 90% of Dextran with a molecular weight of 1,000,000 Dalton (6). In each DFPP procedure, 2,500 ml of plasma was treated and 400-600 ml of the concentrated plasma fraction trapped by the second filter was discarded and replaced with the same amount of 5.8% albumin solution.

Case Report

A 33-year-old Japanese woman was admitted to our hospital on Dec 23, 1987; she was suffering from intermittent fever, bilateral pain in hand joints, knees and shoulders, dyspnea, erythema on the face and extremities. Pericardial effusion was detected by echo cardiology.

The following data were obtained upon admission: total bilirubin, 0.6 mg/dl (normal, 0.2-1.2 mg/dl), aspartate aminotransferase (AST), 53 U/L (normal, 8-30 U/L); alanine aminotransferase (ALT), 57 U/L (normal, 5-35 U/L); gammaglobulin, 1.85 g/dl. Anti-DNA antibody was determined by radioimmunoassay to be 4 U/ml (normal, <6 U/ml). Antinuclear antibody, as measured by fluorescence, was positive at a titer of 1:640 in a speckled pattern. Anti-U1-RNP and anti-Sm were positive at titers of 1:8 and 1:4, respectively. Rheumatoid factor and lupus erythematosus (LE) tests were both negative. CH50 was 41.4 U/ml (normal, 30-50 U/ml).

She was diagnosed as having systemic lupus erythematosus...
(SLE), according to the criteria of the American Rheumatism Association (7). Treatment consisted of 80 mg/day of prednisolone, which was tapered after the improvement of each symptom. However, the serum IgG level gradually increased despite continued administration of prednisolone, 12–20 mg/day.

The first episode of hepatitis, accompanied by high fever, was noted when she was readmitted to the hospital on May 5, 1990, 29 months after the first admission. She had a mild icterus but there were no skin rashes, spider angiomas or palmar erythema. Laboratory findings at the time of admission were as follows: total bilirubin, 3.0 mg/dl; AST, 1,684 U/L; ALT, 1,290 U/L; IgG, 3.053 mg/dl (normal, 800–1,800 mg/dl), C-reactive protein, 8.0 mg/dl (normal, <0.3 mg/dl). Subsequent virus hepatitis serologies [anti-HBs antibody (HBsAb), HBs antigen (HBsAg), anti-HBc antibody (HBcAb), anti-hepatitis C virus antibody (HCVAb), anti-hepatitis A antibody (IgG and IgM), anti-Epstein-Barr virus antibody (IgG and IgM), anticytomegalovirus antibody (IgM)] were all negative. Antinuclear antibody was positive at a titer of 2,560, in a speckled pattern. Anti-U1-RNP and anti-SS-A were positive at a titer of 1:32 and 1:8, respectively. Tests for antibodies to Sm, SS-B, Jo-1, cardiolipin, mitochondria, smooth muscle and cytochrome P450dbl (8) (liver-kidney microsome-1; LKM-1) were all negative. CH50 was 38.1 U/ml; circulating C1q-binding immune complex, 26.7 μg/ml (normal, <34.5 μg/ml).

The patient had no history of blood transfusion, toxin exposure, nor alcohol abuse. Lymphocyte stimulating tests, using several drugs that had been administered to her, were all negative. According to the present illness, past history, and laboratory data, she was diagnosed as suffering from AIH. The hepatitis condition responded well to an increased dose of prednisolone (40 mg/day), which again was gradually tapered down as her condition improved. She was discharged from the hospital on June 7, 1990. However, she suffered from another attack of hepatitis 3 months later and was readmitted to the hospital in September 1990.

The clinical course of events during the period of recurring hepatitis attacks is illustrated in Fig. 1A. Liver biopsy specimens obtained on September 25, 1990, showed plasma cell-dominant inflammatory cell infiltration in the portal area (Fig. 2A). Mizoribine (bredinin) therapy (100 mg/day) was initiated on February 20, 1991, and the patient was discharged several days later.

On March 9, 1991, the patient suffered from a fourth recurrence of hepatitis and was readmitted to the hospital. The decision was made to administer DFPP therapy. However, since a total of 25.9 grams of prednisolone had been administered to the patient over a period of 39 months preceding the onset of the fourth attack, and considering the risk of myopathy and osteoporosis associated with such massive corticosteroid therapy, the DFPP therapy was initiated without increasing the dose of prednisolone.

After the first DFPP procedure, serum IgG decreased from 3,239 mg/dl to 1,948 mg/dl, but it increased to 4,524 mg/dl after 7 days. This rebound effect was again noted after the second DFPP procedure. In addition, total bilirubin increased to a level of 11.6 mg/dl and prothrombin time decreased to 34%. Therefore, methylprednisolone pulse therapy (500 mg on day 1; 250 mg on day 2) was performed concurrently with the third apheresis procedure, which was followed by an oral administration of prednisolone (50 mg/day). After a single plasma exchange therapy (exchanged plasma volume, 2,400 ml) on April 1, six DFPP procedures were performed intermittently over the next 2 months. With these vigorous apheresis procedures combined with immunosuppressive therapies, AST, ALT, total bilirubin, and IgG were normalized; the patient was discharged on June 26, 1991. The course of clinical events during her period of hospitalization is illustrated in Fig. 1B.

After discharge, the patient received DFPP therapy monthly in the outpatient clinic, using a simplified procedure developed in our apheresis center (9). Immunosuppressive agents (prednisolone, 10–20 mg/day; mizoribine (10), 100 mg/day; methotrexate, 7.5 mg/week) were also administered. Serum IgG increased after each DFPP session but never exceeded 2,000 mg/dl (Fig. 1C). There were no attacks of hepatitis in the 18 months following the last (4th) attack. The course of clinical events during the year since her discharge is shown in Fig. 1C.

Liver biopsy specimens obtained on September 30, 1992 showed almost normal features with little inflammatory cell infiltrates (Fig. 2B).

**Discussion**

Although the prototype forms of AIH and SLE differ in clinical, biochemical, serologic, and histologic features as well as in immunogenetic background, there are examples similar to this case wherein features of both diseases coexist and criteria for both are fulfilled (11). As for the features of SLE in this patient, the following points are distinctive: (A) anti-DNA, hypocomplementemia, and nephritis had been negative throughout her clinical course; (B) erythema, arthritis and anti-Sm disappeared about one month after the onset of corticosteroid therapy and has been negative since then.

Prednisolone at 12–20 mg/day is effective for preventing the recurrence of SLE but it is not effective for preventing the complication of AIH. If this patient is treated with prednisolone alone, we suppose 30–40 mg/day of this agent as a maintenance dose should be required for obviating the increase of serum IgG and the recurrence of AIH. DFPP therapy is suitable for removing massive serum IgG and in this meaning, this modality has a 'corticosteroid sparing effect'.

There appears to be no relationship between pericardial effusion and hepatitis. First, the volume of pericardial effusion in this patient was greatest at the time of her first admission, when she showed signs of heart failure as a result of the massive effusion, yet there were no signs of hepatitis at the time. Further, the effusion volume, estimated at about 500 ml changed little after the first discharge, even during the subsequent attacks of hepatitis.

The attacks of hepatitis were not considered to be drug-induced, because lymphocyte stimulating tests using drugs that
Fig. 1. Clinical course of the patient during the several phases of this study. (A) May 1990–March 1991, during which time she suffered from recurrent attacks of AIH; (B) March 1991–June 1991, during which she received DFPP therapy and corticosteroids/immunosuppressants as an in-patient; and (C) July 1991–July 1992, during which drugs and DFPP therapy was administered in the outpatient clinic. Arrows indicate days DFPP was performed. AST: aspartate, aminotransferase, ALT: alanine aminotransferase, T.Bil: total bilirubin, MTX: methotrexate, pred.: prednisolone, =: mizoribine 100 mg/day, *: plasma exchange.
had been administered to her were negative. Further, after DFPP therapy was introduced, new drugs could be administered without provoking further attacks of hepatitis.

The molecular weights (M.W.) of AST, ALT and IgG are 94,000, 116,000 and 146,000, respectively. The first 2 serologic markers of hepatitis were also removed along with IgG by the DFPP system [estimated amount removed (6): AST, 38%; ALT, 48%; IgG, 54%, respectively], especially during the first 4 treatments; thereafter, they were stable and within normal limits throughout the remainder of this study (Figs. 1B, 1C). Whether or not the apparent success of the DFPP therapy was a result of, or a contributor to, the normalization of these serologic markers remains to be determined. Certainly, improvements in clinical symptoms and control of intrahepatic inflammation occurred concomitantly with the removal of these markers and IgG. Serological marker levels have been normal since the last discharge, during which time there have been no occurrences of clinical symptoms (fever, malaise, and icterus).

When DFPP therapy was initiated, serum IgG increased remarkably just after the first 2 procedures. This increase is believed to be due both to excessive autoantibody reproduction provoked by the procedure, and to the refilling phenomenon of IgG from the extravascular pool (e.g., that deposited in the liver) into the circulation (12–14). Treatment with relatively high doses of corticosteroids and/or immunosuppressive agents (as shown in Fig. 1B) is essential to avoid stimulating B cells, especially when DFPP is first introduced. The improvements in clinical and laboratory findings observed in this phase may also have been the result of the administration of these drugs.

However, it is difficult to evaluate precisely the effect of methotrexate alone on the clinical course of AIH in this patient. There has been no recurrence of AIH without administration of this agent for the recent three months since May 1992 (Fig. 1C).

After the last hospital discharge (June 1991), the dosage of prednisolone was reduced and maintained at 10 mg/day because the patient could not tolerate the drug’s adverse effects. During this time, the dosages of corticosteroid and immunosuppressive drugs were not sufficient to suppress IgG production completely (Fig. 1C). In combination with these drugs and monthly DFPP procedures in the outpatient clinic, serum IgG was maintained at less than 2,000 mg/dl; there was no recurrence of hepatitis during the entire 18-month period.

Humoral and cellular autoimmune reactions theoretically can cause hepatocellular damage. Although T-cell recognition of liver antigens is an essential part of the process and T cells are predominant in the inflammatory infiltrate in liver biopsies, direct T-cell cytotoxicity does not seem to occur in AIH (15). Poralla et al have shown that a monoclonal antibody against a liver cell surface antigen can directly cause hepatocyte lysis in vitro (16). Alternatively, autoantibodies, may cooperate with non-T lymphocytes (K cells) in antibody-mediated cellular cytotoxic reactions (15). Our results indicate that reduction of immunoglobulins in the plasma, including pathogenic autoantibodies to the liver, has direct therapeutic implication.

DFPP procedures are decidedly preferable to plasma exchange, since the use of albumin solution for replacement rather than plasma avoids or minimizes the risk of introducing undetected virus infections. As an added benefit, the volume of substitution solution in DFPP is only about 1/5 that of plasma exchange procedures.

This case study shows that DFPP might be an optional modality in the treatment of patients with AIH who are resistant to massive corticosteroid or immunosuppressive drugs, and/or cannot tolerate them because of their adverse effects.

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