Successful Treatment of Encapsulating Peritoneal Sclerosis by Hemodialysis and Peritoneal Lavage Using Dialysate Containing Dissolved Hydrogen

Encapsulating peritoneal sclerosis (EPS) is the most serious and life-threatening complication of peritoneal dialysis (PD) therapy, as mortality is extremely high once it occurs. According to recent reports (1–5), mortality rate of EPS is 14 – 84%. Extensive fibrosing of the peritoneum in patients with EPS leads to symptoms of malnutrition and small bowel obstruction (ileus). Encapsulation can progress so that the bowel eventually becomes completely cocooned. The outcomes of several medical approaches such as tamoxifen, steroids, and newer immunosuppressive agents to retard EPS progression (6) remain poor. Moreover, in some alive cases, surgical approach (enterolysis, peritonectomy) is inevitable to cure symptoms of ileus (6).

Dissolved hydrogen (H_2) has a unique biological antioxidative and anti-inflammatory capacity (7). Accumulating evidence suggests that H_2 ameliorates organ damage in various models of ischemia and inflammation (8). Clinical applications of H_2 to pro-inflammatory disorders have been investigated, particularly for use during hemodialysis (HD) therapy (9–15). In addition, we recently showed that peritoneal dialysate containing high H_2 concentrations could reduce both peritoneal and systemic oxidative stress in the clinical setting (16).

In the present case study, dialysate enriched with H_2 for both hemodialysis (HD) therapy and peritoneal lavage caused symptoms and laboratory signs of EPS to decrease.

CASE HISTORY

A 63-year-old Japanese man with a 6-year history of continuous ambulatory peritoneal dialysis (CAPD) presented to our emergency room with constipation and nausea of 7 days' duration.

The patient had been diagnosed with diabetes mellitus at the age of 40, and had begun PD at the age of 57. Peritoneal permeability in the fast peritoneal equilibrium test remained at a high average. He had been prescribed with 2.27% glucose dialysate (2 L/bag, 2 bags/day) and 7.5% icodextrin dialysate (2 L/bag, 1 bag/day). He had no past history of infectious peritonitis nor hemoperitoneum.

Defecation ability ceased 7 days before presenting at our emergency room with constipation and nausea. His blood pressure was 155/80 mmHg, pulse 70 beats/min and temperature 37.8°C. His abdomen was distended with slight diffuse tenderness. A glycerin enema failed to elicit bowel movement and he was admitted with suspected EPS. Table 1 shows the laboratory findings. Inflammatory markers (white blood cells and C-reactive protein [CRP]) were elevated (12,600 /μL and 23.62 mg/dL, respectively). Effluent fluid was slightly cloudy with elevated numbers of white blood cells in the sediment. Infectious peritonitis was tentatively diagnosed based on these findings.

TABLE 1
Laboratory Data Upon Admission

Blood findings	
White blood cells	12,600/μL
Red blood cells	371×10^4/μL
Hemoglobin	12.0 g/dL
Hematocrit	34.0%
Platelets	14.9×10^4/μL
Total protein	5.2 g/dL
Albumin	2.9 g/dL
Total billirubin	0.26 mg/dL
Aspartate aminotransferase	15 IU/L
Alanine aminotransferase	13 IU/L
Lactate dehydrogenase	286 IU/L
Gamma-glutamyl transpeptidase	8 IU/L
Urea nitrogen	89.6 mg/dL
Creatinine	15.69 mg/dL
Uric acid	7.6 mg/dL
Sodium	121 mEq/L
Chloride	87 mEq/L
Potassium	5.2 mEq/L
Calcium	8.2 mg/dL
Inorganic phosphorus	4.3 mg/dL
C-reactive protein	23.62 mg/dL
Culture	Negative
Effluent fluid (sediment) findings	
Red blood cells	>100/HPF
White blood cells	>500/HPF
Mesothelial cells	(-)
Bacteria	(+)
Culture	Negative

HPF = high-power field.

The patient's oral intake was stopped and total parenteral nutrition was started. Peritoneal therapy was discontinued and hemodialysis (HD) was started on hospital day 3. The patient had nausea that was not improved by intravenous ceftazidime and the effluent remained cloudy. Repetitive effluent fluid culture remained negative.

The peritoneal catheter was laparoscopically removed and re-implanted on hospital day 10. A laparoscopic examination revealed that the intestine was encapsulated by a thin white membrane (Figure 1). Figure 2A shows the histological

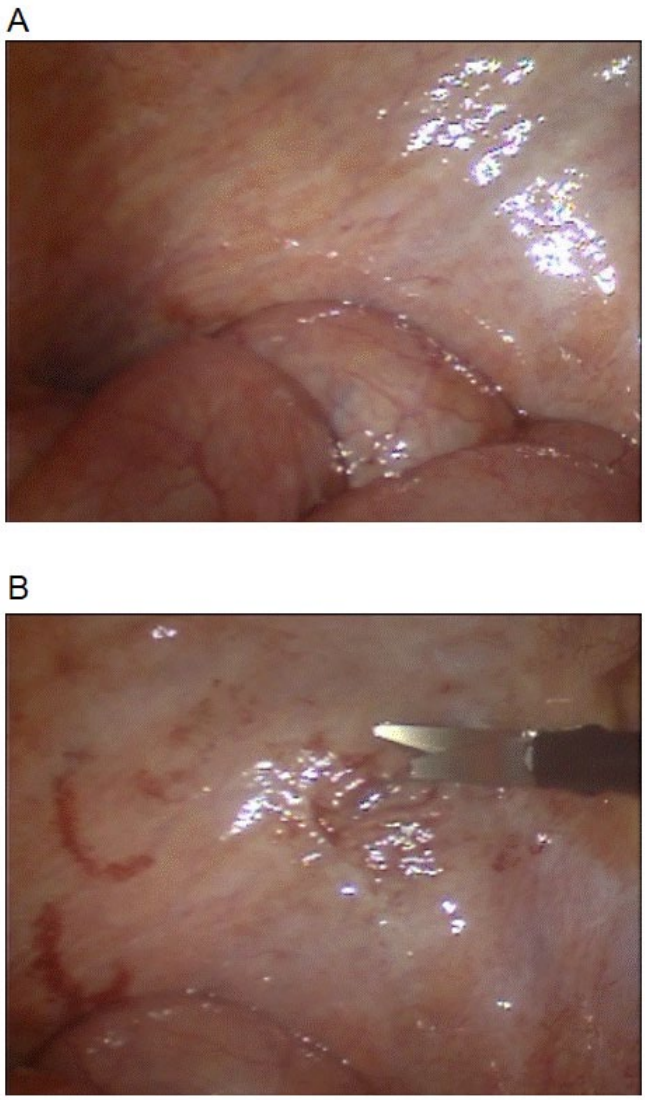

Figure 1 — Macroscopic findings at laparoscopic examination. (A) Both visceral and parietal peritonea are whitish and thickened. Intestine is encapsulated by thin membrane. (B) Specimen of parietal peritoneum obtained under laparoscopic monitoring. 254×366mm (72 × 72 DPI)

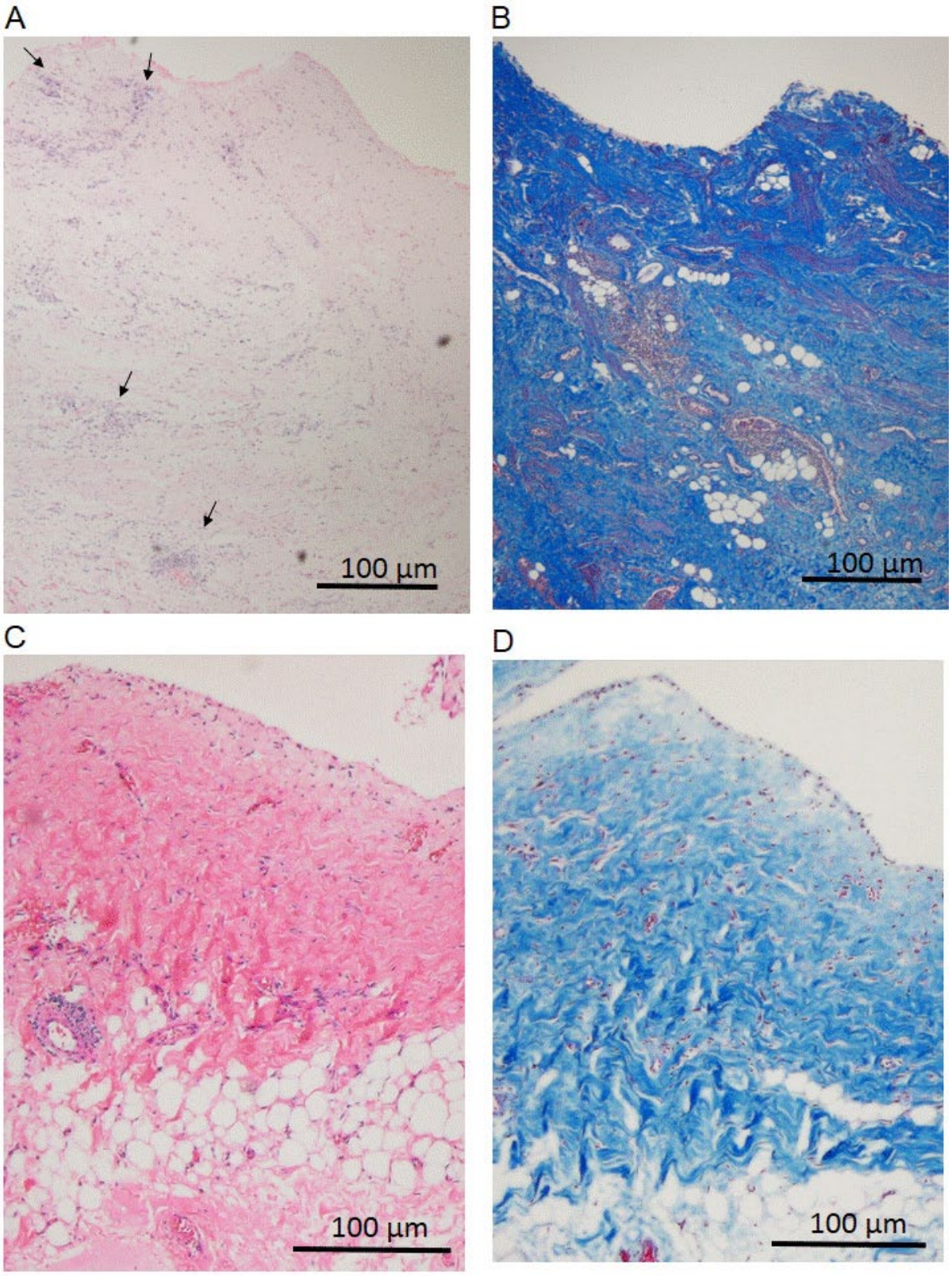

Figure 2 — Histological findings of parietal peritoneum before (A, B) and after (C, D) treatment with hydrogen-enriched dialysate. (A) Thin membrane covering peritoneum consists mainly of homogeneous or lamellar fibrinous material containing fibroblasts stained with hematoxylin and eosin (HE). Mononuclear cell infiltration is visible in some areas (arrowheads). (B) Fibrinous materials (red or blue with Masson trichrome stain) suggest fibrin or organized fibrin components. (C) Sub-mesothelial connective tissue (compact zone) has become obviously thinner after treatment with H_2 (mean: 190 µm; HE stain). (D) Surface is covered by mesothelial monolayer and fibrinous materials are absent (Masson trichrome stain). 254×366mm (72 × 72 DPI)

findings of a biopsy specimen from the parietal peritoneum (hemotoxilin-eosin stain). Visualization using Masson trichrome revealed a peritoneal surface that was up to 2,000 μm thick and mainly comprised red or blue homogeneous or lamellar fibrinous material containing scatted fibroblasts. Figure 2B shows fibrin or organized fibrin components. Mesothelium was not identified. These findings and the clinical course indicated a final diagnosis of EPS. Prednisolone (30 mg/day) combined with peritoneal lavage using peritoneal dialysate somewhat improved the nausea and decreased the serum CRP level. However, the nausea worsened and CRP became elevated when the prednisolone dose was reduced to 20 mg/day on hospital day 21.

Considering the possible contribution of oxidative stress on the pathogenesis of EPS, HD using H_2-enriched dialysate (12) was started on hospital day 31. This decreased the CRP value (Figure 3) and improved the nausea. Oral intake was started on hospital day 38 without the recurrence of nausea. Peritoneal lavage using H_2-enriched peritoneal solution was started on hospital day 40 to minimize peritoneal damage as described (16). This strategy obviously diminished the cloudiness of the effluent fluid due to blood (Figure 3). The prednisolone dose was gradually tapered to 0 by hospital day 77 and the patient was discharged on hospital day 94.

Two months later, the peritoneal catheter was laparoscopically removed and a peritoneal biopsy was obtained. Intestinal encapsulation was not evident. The mean thickness of the sub-mesothelial connective tissue (compact zone) was 190 μm, and it was covered by a monolayer of mesothelial cells (Figure 2C and D). The patient has remained free of signs of EPS including ileus until now (for 18 months after the catheter removal).

DISCUSSION

This case study showed that delivering H_2 via HD and peritoneal lavage, in addition to oral prednisolone therapy, ameliorated EPS. Thus, H_2 might have potential as a novel medical treatment for EPS. We cannot point out the definitive trigger of EPS occurrence in this case. However, the possible contribution of bacterial translocation (profound bacterial peritonitis) might be considered.

Several case reports have described medical treatment of EPS using mainly tamoxifen and/or corticosteroid (17–20). One case-control study found that prophylactic tamoxifen suppressed EPS occurrence (21), and a nationwide cohort study in Japan showed that corticosteroid therapy caused 38.5% of EPS to go into remission (22). However, harmful effects such as ischemic stroke and pulmonary embolism are associated with tamoxifen and opportunistic infection is associated with corticosteroid. In contrast, H_2 has been tested particularly in the field of deepwater diving, and no toxicity was identified even at high concentrations (23). Thus, H_2 has therapeutic potential for pathological states that are related to oxidative stress and inflammation (24).

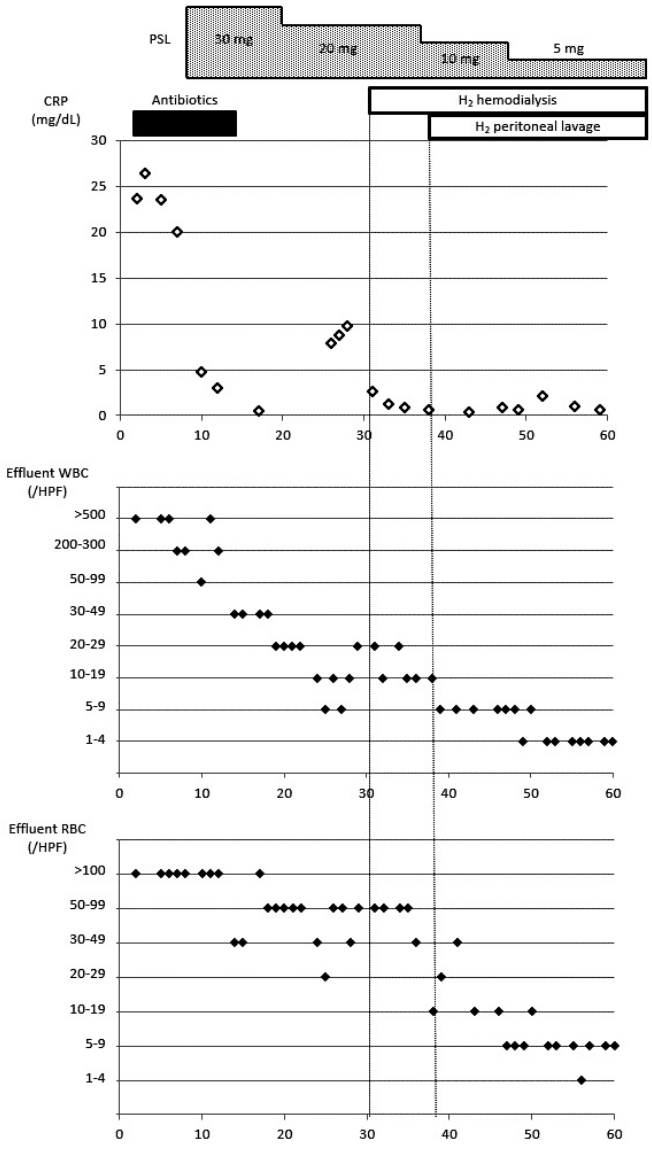

Figure 3 — Course of serum C-reactive protein and effluent white and red blood cells. 254x366mm (72 × 72 DPI) CRP = C-reactive protein; WBC = white blood cells; RBC = red blood cells; HPF = high-power field.

Dissolved hydrogen had been regarded as chemically inactive until the discovery of its antioxidant effects (5). Since then, accumulating reports have indicated that H_2 could be a useful new therapeutic modality in many biomedical fields. Consuming H_2-enriched water exhibits anti-oxidative capabilities without detrimental effects in experimental (25–29) and clinical settings, including type II diabetes mellitus (30), metabolic syndrome (31), myopathies (progressive muscular dystrophy and polymyositis/dermatomyositis) (32), and rheumatoid arthritis (33). In addition, we also reported the clinical feasibility of using H_2-enriched water as the dialysate for HD (13–15) and PD (16). The findings of these previous reports and the present case study indicate that H_2 delivered via HD and peritoneal lavage could be useful as a novel medical treatment for EPS. In addition,

regular use of H_2-enriched peritoneal dialysate might be an interesting focus of clinical trials from the viewpoint of peritoneal preservation.

CONCLUSION

The present case report shows the efficacy of delivering H_2 via HD and peritoneal lavage in EPS treatment. This experience suggests that hydrogen has potential as a novel medical treatment for EPS, and thus further investigation regarding this treatment is warranted.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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