Tohoku J. Exp. Med., 1998, **185**, 147-155

Case Report

A Case of Hemolytic Uremic Syndrome Associated with Emphysematous Cholecystitis and a Liver Abscess

KAZUNORI YOSHIDA, MASAHIRO ARAKAWA,[1] SHYUICHI ISHIDA[1] and YASUHIKO SASAKI[1]

Section of Internal Medicine and Disability Prevention, Disability Science, Tohoku University Graduate School of Medicine, Sendai 980-8574, and [1]Department of Internal Medicine, Ishinomaki Red Cross Hospital, Ishinomaki 986-0015

YOSHIDA, K., ARAKAWA, M., ISHIDA, S. and SASAKI, Y. *A Case of Hemolytic Uremic Syndrome Associated with Emphysematous Cholecystitis and a Liver Abscess.* Tohoku J. Exp. Med., 1998, **185** (2), 147-155 —— Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. Most cases of HUS are characterized by a prodromal phase of diarrhea and melena, and affect mainly children. Here we report a unique case of adult-onset HUS that was associated with emphysematous cholecystitis and a liver abscess. The patient did not suffer from diarrhea or melena on admission, but abdominal CT scans revealed emphysematous cholecystitis and a liver abscess. Cholecystectomy was performed and the liver abscess was drained. Cultures of the bile and liver abscess contents were negative, but the serum samples had antibodies against *Escherichia coli* (*E. coli*) O157. The patient was anuric for 14 days, and underwent hemodialysis that was repeated 15 times and plasma exchanges 6 times. She recovered from acute renal failure but with inadequate urinary concentrating ability as a sequela. Histopathological examination of renal biopsy specimens on the 83rd hospital day revealed almost normal glomeruli and patchy atrophy of tubules with an increase of interstitium. This is a very rare case of HUS associated with emphysematous cholecystitis and a liver abscess successfully treated with aggressive supportive care. It is possible that an infection with verotoxin-producing *E. coli* O157 caused the disease. ——
hemolytic uremic syndrome; cholecystitis; liver abscess; *Escherichia coli* O157; verotoxin

The hemolytic uremic syndrome (HUS) is a syndrome consisting of acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia. HUS affects mainly children and is characterized by a prodromal phase of diarrhea and

Received April 23, 1998; revision accepted for publication June 30, 1998.

Address for reprints: Kazunori Yoshida M.D., Section of Internal Medicine and Disability Prevention, Disability Science, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan.

melena. *Escherichia coli* (*E. coli*) O157 produces verotoxin and causes diarrhea, hemorrhagic colitis and HUS. In the summer of 1996, an unexpectedly large number of outbreaks of food poisoning due to *E. coli* O157 occurred in Japan. In addition, many sporadic cases of *E. coli* O157 infection were also reported and a total of about 8400 patients were recorded during that year (Takeda 1997). We report a unique case of adult-onset HUS associated with emphysematous cholecystitis and a liver abscess successfully treated with supportive care.

Case Report

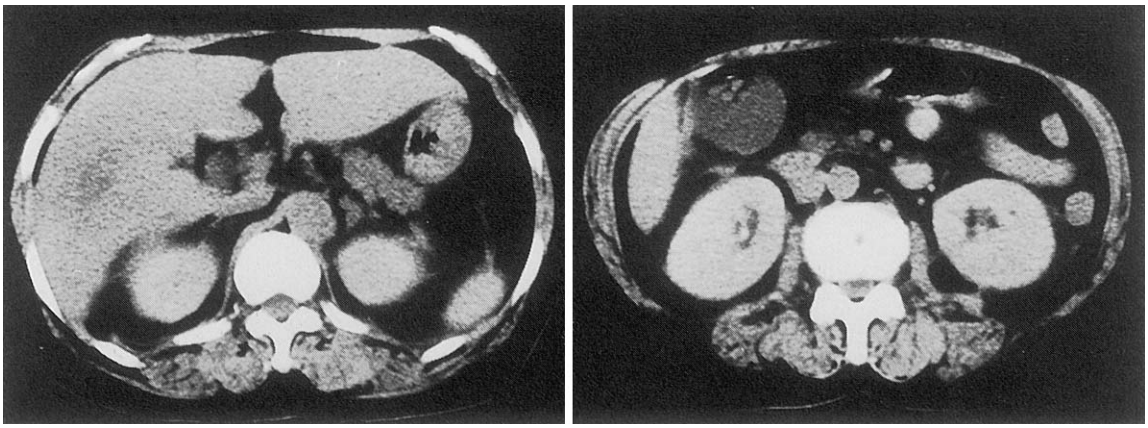
A 67-year-old woman developed abdominal discomfort on June 20, 1994. On the next day she had upper abdominal pain, nausea and vomiting. Her symptoms exacerbated on June 22, and she sought medical treatment at a hospital. Laboratory findings revealed leukocytosis, increases in the lactate dehydrogenase and aminotransferase activities, and serum urea nitrogen and creatinine contents. On June 23, 1994, laboratory data indicated deterioration of her conditions, which was substantiated by the clinical picture. At this time she was transferred to our hospital. There was no record of previous liver or renal disease. She was alert and oriented, but appeared acutely ill. Her physical examination upon admission indicated the following: body height, 147 cm; body weight, 57 kg; respiration rate, 30/minute; body temperature, 37.5°C; pulse rate, 84/minute; and blood pressure 172/90 mmHg. She was severely jaundiced without cutaneous hemorrhage. Heart and respiratory sounds were normal. The upper abdomen was moderately distended and tender, but no rebound tenderness was detected. The liver was palpable 5 cm below the right costal margin but the spleen could not be felt. Her extremities were free of edematous conditions. The results of neurologic examinations were negative. The electrocardiogram was normal with a heart rate of 77/minute. A thoracic roentgenogram revealed mild cardiomegaly with no infiltrates of effusions. The results of the laboratory examinations upon admission are summarized in the Table 1. Marked leukocytosis and mild anemia were observed. The peripheral blood smear showed anisocytosis and fragmentation of the red cells, and toxic granules in the neutrophils. The color of plasma was deeply red and an indirect bilirubin dominant increase of serum bilirubin was observed. The lactate dehydrogenase level was extremely high. These data were suggestive of microangiopathic hemolytic anemia. Increases in the serum total protein and α_2-globulin levels may suggest the presence of massive hemoglobin in the serum. Prothrombin time and activated partial thromboplastin time were prolonged, together with an increase in fibrin degradation products. There was no evidence of hepatitis type A, B or C. Urine exhibited a cola-like color. Urinalysis revealed 3+ positive occult blood, but the sediment contained no red cells. The presence of urinary protein and urobilinogen could not be determined by a test tape method because of massive occult blood. The renal function was impaired. Her stool was brown and negative for occult blood. Direct and

TABLE 1. *Laboratory data on admission*

Blood cell counts		Blood chemistry		Serological test	
White-cell count	51 700/μl	Total bilirubin	8.0 mg/100 ml	C-reactive protein	37.8 mg/100 ml
Differential count		Direct bilirubin	2.3 mg/100 ml	ANA	negative
band forms	21.5%	Indirect bilirubin	5.7 mg/100 ml	C_3	79 mg/100 ml
segment forms	76.0%	AST	988 IU/liter	C_4	24 mg/100 ml
lymphocytes	0.5%	ALT	476 IU/liter	CH_{50}	42.7 U/ml
monocytes	2.0%	LDH	13 886 IU/liter	IgM-HA	negative
toxic granule	positive	γ-GTP	87 IU/liter	HBs antigen	negative
Red-cell count	$261\times10^4/\mu$l	Total cholesterol	128 mg/100 ml	HCV antibody	negative
reticulocyte	2%	Total protein	10.1 g/100 ml		
anisocytosis	positive	albumin	39.7%	Direct Coombs	negative
fragmentation	positive	α_1-globulin	3.3%	Indirect Coombs	negative
Platelet count	$57.8\times10^4/\mu$l	α_2-globulin	47.4%	Ham test	negative
Hemoglobin	10.7 g/100 ml	$\beta+\gamma$-globulin	0.97%	Sugar-water test	negative
Hematocrit	22.2%	Urea nitrogen	76.0 mg/100 ml		
ESR	36 mm/hr	Serum creatinine	2.8 mg/100 ml	Urinalysis	
		Uric acid	3.4 mg/100 ml	Protein	not determined
Coagulation profile		Glucose	288 mg/100 ml	Glucose	+
PT	41%	Na	128 mEq/liter	Occult blood	##
APTT	51.3%	K	3.9 mEq/litter	Urobilinogen	not determined
fibrinogen	480 mg/100 ml	Cl	98 mEq/liter	Sediments	
FDP	78.8 μg/100 ml	Ca	4.6 mEq/liter	red cells	0/HPF
		P	4.8 mg/100 ml	white cells	1-4/HPF
		Creatine kinase	667 IU/liter	epithels	5-9/HPF
		Amylase	228 IU/liter	casts	0/HPF

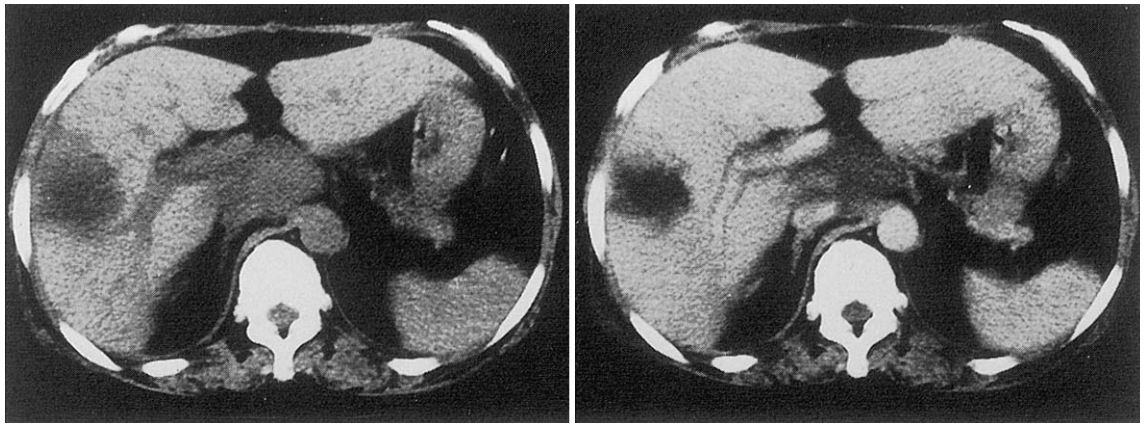
ESR, erythrocyte sedimentation rate; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fiblin degradation products; AST, aspartate Aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltranspeptidase; ANA, antinuclear antibody; HPF, high power field.

indirect Coombs' tests were negative. The results of the Ham test and sugar-water test were also negative. Based on these results, autoimmune hemolytic anemia and paroxysmal nocturnal hemoglobinuria were ruled out. An analysis of the arterial blood gases at ambient indicated the following: pH, 7.387; PCO_2, 26.0 mmHg; PO_2, 67.0 mmHg; bicarbonate, 15.8 mEq/liter and base excess −7.4. Abdominal CT scans of June 23, revealed a swollen gallbladder with an air layer within and a low density area in the right hepatic lobe (Fig. 1). Emphysematous cholecystitis was diagnosed. Because enhanced CT scans were not obtained due to an impaired renal function, a quantitative diagnosis of the low density area of the liver was not made. Despite adequate hydration and intermittent intravenous furosemide administration, her blood urea nitrogen and creatinine levels were elevated. On June 24, 1994, a cholecystectomy was performed under general anesthesia and she was subjected to hemodialysis. On June 25, she became oliguric, with urine output amounting to less than 400 ml/day. On June 26, her hemoglobin content and platelet count fell to 6.0 g/100 ml and $9.6 \times 10^4/\mu l$, respectively. A diagnosis of hemolytic uremic syndrome was made on the basis of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. On June 27, 1994, she was subjected to hemodialysis, and plasma exchange with 2800 ml of fresh frozen plasma. She received ventilatory assistance from June 24 to June 28. On July 5, 1994, unenhanced and enhanced abdominal CT scans were obtained, followed by hemodialysis (Fig. 2). The low density area of the liver was enlarged in comparison with that seen on the first day of hospitalization. The margin of the low density area was enhanced. A diagnosis of liver abscess was made. On July 6, the abscessed liver was drained percutaneously, followed by irrigation using a saline containing penicillin G. Plasma C-reactive protein content and white blood cell count were 13.5 mg/100 ml and 17 700/μl, respectively, on the day of liver abscess drainage. Plasma C-



a b

Fig. 1. Abdominal CT scans obtained on June 23, 1994. (a) Unenhanced CT scan demonstrated a low density area in the right hepatic lobe. (b) Unenhanced CT scan demonstrated a swollen gallbladder with an air layer inside.



a b

Fig. 2. Abdominal CT scans obtained on July 5, 1994. (a) Unenhanced CT scan demonstrated a low density area in the right hepatic lobe, which was bigger than that of June 23, 1994. (b) Enhanced CT scan demonstrated that the margin of the low density area of the liver was enhanced, suggestive of a liver abscess.

reactive protein content decreased dramatically to 7.3 mg/100 ml on July 7, and white blood cell count decreased to 8900/μl, less than 10 000/μl for the first time, on July 12. She required 15 hemodialysis treatments, 6 plasma exchange treatments, and 8 transfusions of packed red cells. She was anuric from June 29 to July 12, but became polyuric on July 23, two days after the last hemodialysis. She had transit proteinuria with a maximal value of 1.2 g/day during the recovery phase of acute renal failure. Her plasma lactate dehydrogenase level was normalized on July 12, four days after the last plasma exchange. The time course of the patient's clinical events and laboratory data are summarized in Fig. 3. The cultures of the blood, bile from the resected gallbladder and liver abscess content were negative. Her serum samples of July 1 and 21 showed the presence of antibodies against the native antigen of *E. coli* O157 with a titer of 1 : 100 (Yamada et al. 1994). Her condition improved with resolutions of the jaundice, microangiopathic hemolytic anemia, and acute renal failure.

On September 13, 1994, an open renal biopsy was performed. At that time her creatinine clearance was 56 ml/minute and the results of urinalysis were normal. Histopathological examination revealed almost normal glomeruli and patchy atrophy of tubules with an increase of interstitium. The epithelial cells of the proximal tubules showed vacuolation. Some epithelia of the tubules, mainly the proximal tubules, contained hemosiderin. Arterioles and small arteries were normal (Fig. 4). Fishberg's urine concentration test gave a maximal urinary specific gravity of 1.014 (474 mOsm), which suggest a deficiency of urine concentrating ability. A phenolsulfonphthalein test (Chapman-Halsted method) gave a value of 15.9% at 15 minutes. The results of these renal function tests could be interpreted to reflect the histological findings.

She had to consume an adequate amount of water to maintain urine output

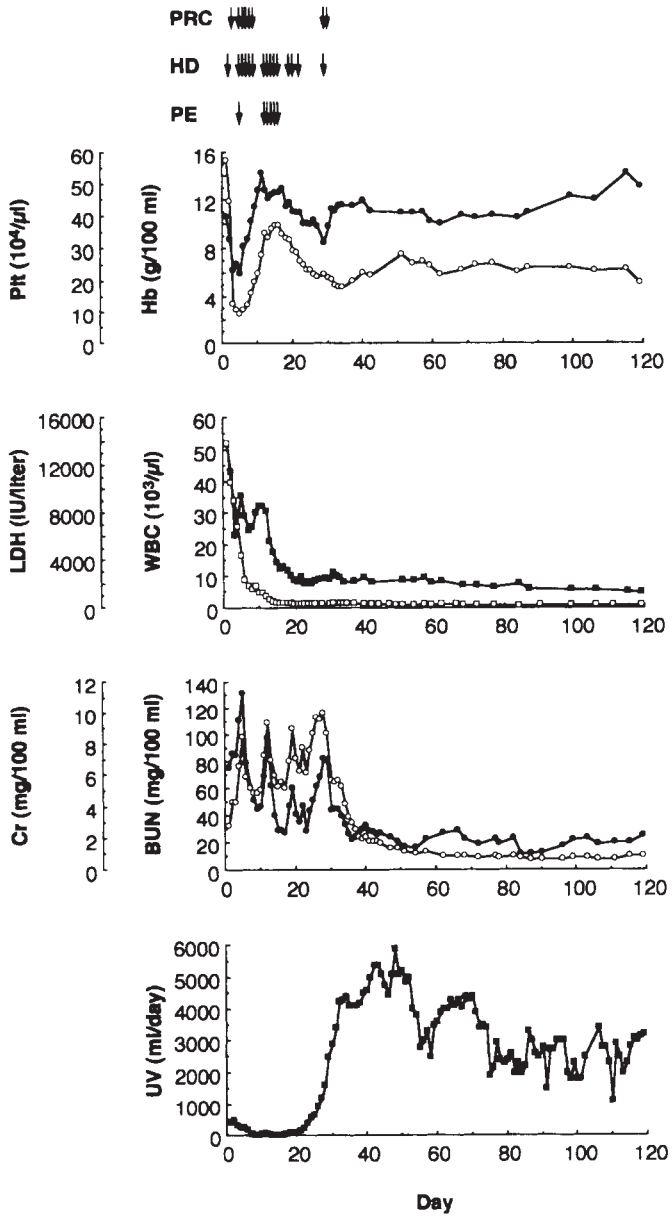


Fig. 3. The time course of the patient's clinical events and laboratory data. PRC, packed red cells; HD, hemodialysis; PE, plasma exchange; Plt (○), platelet count; Hb (●), hemoglobin; WBC (■), white cell count; LDH (□), lactate dehydrogenase; BUN (●), blood urea nitrogen; Cr (○), serum creatinine; UV, urine volume.

above 2500–3000 ml/day and avoid volume depletion. She was discharged home from 122 days of hospitalization. She remains well three years after this acute illness.

Discussion

Several possible causative agents of HUS have been reported, including bacterial or viral infections, use of certain drugs, pregnancy, and renal diseases. The typical HUS is likely to occur in childhood, usually in association with a prodromal phase of diarrhea and melena (Remuzzi and Ruggenenti 1995; Su and

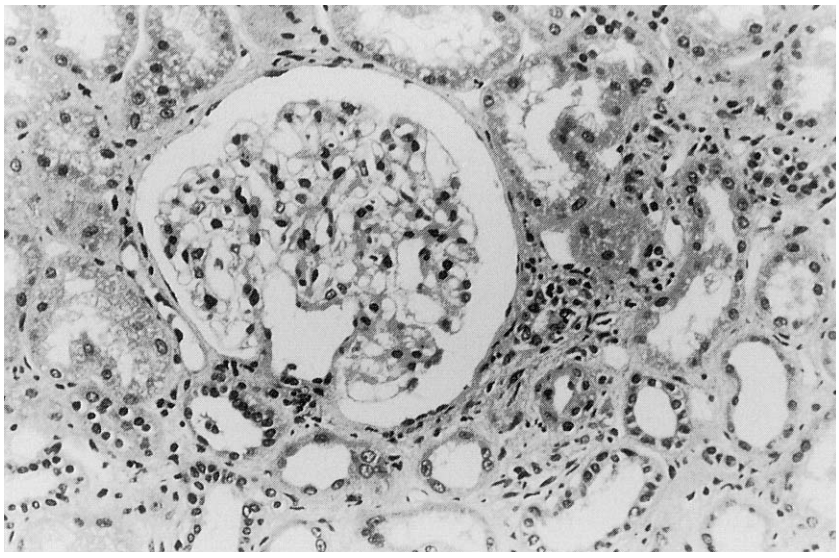


Fig. 4. Renal biopsy on day 83 of hospitalization, demonstrating almost normal glomerulus and patchy atrophy of tubules with an increase of interstitium. Hematoxylin-Eosin stain $\times 200$.

Brandt 1995). The commonest cause of this form of HUS is a verotoxin-producing bacterium such as *E. coli* O157: H7 (Karmali et al. 1983; Griffin et al. 1988), or a shiga toxin-producing *Shigella* bacterium (O'Brien and Holmes 1987). In the present case, the patient did not suffer from diarrhea or melena, but emphysematous cholecystitis and a liver abscess were present. Liver involvement with hepatomegaly and increased aminotransferase activities can occur (Van Rhijn et al. 1977), and rare cases of cholestasis have been reported (Jeffrey et al. 1985) in HUS. As far as we know, there is only one case of HUS that was associated with cholecystitis (Babott et al. 1980) and no case of HUS that was associated with a liver abscess. Cultures of the bile and liver abscess contents were negative, but the patient's serum showed the presence of antibodies against *E. coli* O157. Therefore it is strongly suggested that this case of HUS was caused by an infection with *E. coli* O157.

Several unfavorable prognostic factors have been reported in HUS. The prognosis of adult-onset HUS is not as favorable as that of HUS in children (Morel-Maroger et al. 1979; Carter et al. 1987). An unfavorable prognosis of polynuclear cell levels over 20 000/μl on admission has been reported (Walters et al. 1989). A poor prognosis has also been reported in relation to an initial anuria over 8 days (Loirat et al. 1993; Tönshoff et al. 1994), and an exaggerated lactate dehydrogenase activity (Ruggenenti and Remuzzi 1990). Taken together, the present case does indeed represent a very severe HUS, but the patient recovered with minimal residual renal defect.

No specific treatment currently exists for HUS associated with *E. coli* O157 infection other than supportive therapy (Su and Brandt 1995). Correction of fluid and electrolyte abnormalities by dialysis has probably had a major role in

the overall improvement of short-term survival in HUS. Antimicrobial agents have not been shown to modify the illness, but few conclusive data are available on individual agents (Remuzzi and Ruggenenti 1995). In the present case, however, liver abscess drainage and irrigation with penicillin G seemed to have beneficial effects on the patient's clinical course. A general consensus credits the use of plasma infusion or plasma exchange in adults and in all forms of HUS with neurological involvement. However, although plasma manipulation induces prompter hematological remission, it is not clear whether the manipulation has an effect on renal recovery (Remuzzi and Ruggenenti 1995). There is no consensus on the therapeutic value of heparin, fibrinolysis therapy, prostacyclin, corticosteroids, or agents that inhibit platelet aggregation in HUS. Until new strategies, including orally administered toxin-binding resins and active or passive immunization, become available in clinical practice, the general consensus for the moment is that careful supportive management is still the most appropriate form of treatment.

The most frequent lesion in the early course of HUS is glomerular thrombotic microangiopathy (Loirat et al. 1993; Remuzzi and Ruggenenti 1995). It is characterized by thickening of the glomerular capillary walls, which have a double-contour appearance. The tubules are often atrophic, may show necrosis, and contain hyaline casts and red cells. The interstitium is edematous or fibrous and, in some cases, contains scattered chronic inflammatory cells. Arteries and arterioles show thrombotic microangiopathy. Lingwood (1994) demonstrated that verotoxin binding was detected within the glomerulus of infants but not within that of adults, and that verotoxin binding was primarily detected within distal tubules and collecting ducts in both types of kidneys. These findings may provide a key link for the age-related incidence of HUS following verotoxin infections. In the present case, renal histology on day 83 of hospitalization revealed almost normal glomeruli and patchy tubulo-interstitial changes. Because the patient was seriously ill on admission, a renal biopsy was not performed in the earlier phase, but the histological and functional findings of the case might be consistent with the findings of Lingwood (1994) mentioned above.

In summary, we have reported a unique case of adult-onset HUS that was associated with a liver abscess and emphysematous cholecystitis. Cultures were negative for *E. coli* O157, but serum samples contained antibodies against the organism. Histological examination of the renal biopsy specimens revealed patchy tubulo-interstitial changes. This may explain the urine concentration defect as a sequela of the case.

Acknowledgment

We are grateful to Ms. Akemi Kai, Department of Microbiology, Tokyo Metropolitan Research Laboratory of Public Health, for the determination of antibodies against *E. coli* O157.

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