CLINICO-PATHOLOGICAL CONFERENCE

Hemophagocytic syndrome associated with fulminant hepatitis A: a case report

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Abstract. A 37-year-old man had a sore throat and pyrexia since January 1999. He was treated at a nearby hospital, but not improved. Jaundice was indicated there, and the patient was referred transferred to our hospital, where he was admitted for treatment with a diagnosis of severe acute hepatitis with acute renal failure. Thereafter the patient was revealed to have had a past history of heavy drinking, and he underwent the treatment with a diagnosis of acute fulminant hepatitis due to hepatitis A virus (HAV). He showed a tendency toward improvement. During the course, however, viral associated hemophagocytic syndrome (VAHS) developed. Various treatments were conducted, but it was not improved, and the patient died on Hospital Day 66. On pathologic autopsy, remarkable hepatosplenomegaly associated with marked bone marrow abnormalities compatible with VAHS was observed. Aspergillus abscesses were also observed in many organs, and they were considered as an adverse reaction to potent immunosuppressive therapy. Since there have been only a few reports on HAV-related VAHS, discussing VAHS related to HAV, the present case was considered valuable. (Keio J Med 52 (1): 38–51, March 2003)

Key words: hepatitis, viral associated hemophagocytic syndrome, fulminant hepatitis, heavy drinking, aspergillosis

Doctor Ishii (Moderator): Let me declare the 1051st clinicopathological conference open.

The patient under discussion today is a 37-year-old man, whose disease followed a serious clinical course. The period from the diagnosis of the disease until the time of death of the patient was approximately only 50 days. He manifested a series of clinical symptoms during the clinical course, and we had much difficulty in treating him.

So, let us start with the case presentation.

Dr. Yamagishi (Internal Medicine): The patient was a 37-year-old man, whose presenting clinical features were pyrexia, jaundice and hepatic disorder.

Before I begin with the history of his present illness, let me mention that he had been documented to have hyperlipidemia several times in company medical examinations since he was about 28 years old. He was a habitual alcohol drinker; who had been drinking 6–7 whiskey-and-waters 3–4 times a week since he was about 30 years old, and gin, vodka, and other alcoholic beverages, in addition, since he was about 32 years old. In addition to the daily heavy drinking, he had also indulged in intemperate and immoderate eating during the year-end holiday between the end of 1998 to the beginning of 1999; while also drinking heavily, he had eaten fish and shellfish every day during this period. He developed a febrile sore throat and started to have gastric discomfort from January 4, 1999, and visited a nearby hospital on January 7. Acetaminophen (a medicine for fever), eprazinone hydrochloride (a cough medicine) and Ciprofloxacin (an antibiotic) were prescribed, and he took the medications for 5 days. At this time, he had shown transient improvement in response to the treatment given.

However, on January 21, the patient developed a high fever (39.4°C) and arthralgia. He visited another

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nearby hospital on January 22. He was diagnosed to have an upper respiratory tract infection caused by the influenza virus, and an antibiotic was administered intravenously by drip infusion. Concomitantly, he also received the following medication: cefdinir (an antibiotic), diclofenac sodium (an antipyretic), ambroxol hydrochloride, teprenone, domperidone, an expectorant. His symptoms however, did not resolve. He reported passing high-colored urine from January 23, and developed anorexia and general fatigue on January 25.

On the following day, on January 26, he found it difficult to even drink water and could not take any oral medication. He developed right hypochondrial pain, and frequent vomiting and diarrhea, and again visited the nearby hospital. Hematological examination at that time revealed marked liver dysfunction, with a serum GOT of 14,500 IU/L and serum GPT of 10,800 IU/L. The patient was therefore referred to Kitasato Institute Hospital. From there, with the suspected diagnosis of severe acute hepatitis, he was transferred to our hospital and admitted to the GICU ward.

His past history was unremarkable, except for the frequent documentation of hyperlipidemia in company health examinations. There was no history of blood transfusion.

The patient was a heavy alcohol drinker, and had a long history of having a few glasses to half a bottle of low-class distilled spirits daily. As mentioned above, he had been drinking rather heavily since he was about 30 years old. He also smoked about 20 cigarettes a day. In regard to his occupational history, he edited video films for a TV channel. There was no history of allergy.

In the family history, the patient's father had gastric cancer and gallstones.

Dr. Ishii: Thank you, Dr. Yamagishi. We just heard from Dr. Yamagishi the chief complaints, history of present illness, past history, personal history and family history of today's patient. In brief, the patient was a 37-year-old man who was a habitual very heavy alcohol drinker. He gave a history of intemperate eating and drinking every day during the New Year's holiday between the end of 1998 and the beginning of 1999. In the first week of January 1999, he developed gastric discomfort and other symptoms, and had received medication from a local hospital, with some transient improvement. As may be expected, the quantity of alcohol consumed had reduced during this period, but he still continued to drink. About 2 weeks later, he developed a high fever (39.4°C), and received treatment for a suspected diagnosis of influenza virus infection from another local hospital.

Dr. Yamagishi, what exactly was the drug administered by intravenous drip infusion at this time, and what exactly were the other medications administered on this occasion? Antibiotics and what internal medicines?

Dr. Yamagishi: They were antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). A medicine for the stomach discomfort was also used.

Dr. Ishii: And the symptoms did not resolve with this treatment. On the contrary, the patient developed anorexia, dizziness, nausea, diarrhea, and high-colored urine despite the treatment. Was that the reason the patient visited the same hospital again?

Dr. Yamagishi: Yes. He visited this hospital on January 21 and 26. On January 7, however, he had visited another hospital.

Dr. Ishii: We were surprised indeed to hear that the laboratory examination revealed a GOT of 14,500 IU/L and a GPT of 10,800 IU/L. Does anybody have anything more to ask until this point in the course of the patient's illness?

Mr. Igarashi (6th-year student): This patient was referred to our hospital on January 26? Had he been detected to have hepatic dysfunction on earlier health examination or other examinations?

Dr. Yamagishi: No, serum aminotransferases (GOT and GPT) had been normal earlier.

Mr. Izumi (6th-year student): The patient had frequent vomiting and diarrhea according to the report. Could we have some more information regarding the color and other characteristics of the stools?

Dr. Yamagishi: No specific findings had been recorded before admission, but after admission, his records show that he passed white stools.

Dr. Ishii: Did he ever have bloody stools?

Dr. Yamagishi: No, he never had either bloody stools or tarry stools.

Mr. Izawa (6th-year student): With regard to the right hypochondrial pain, had he ever had similar pain before? Also, could you let us know if the hypochondrial pain was persistent or intermittent, and colicky or dull.

Dr. Yamagishi: No, he had never had such pain before. When he was examined at our hospital, severe right hypochondrial tenderness was noted. His pain was dull, although he reported intermittent increase in its severity.

Dr. Ishii: Mr. Izawa, yes, it is very important to know about the characteristics of the pain. It is a good question, but may I ask exactly why you enquired about the characteristics of the pain?

Mr. Izawa: This patient had been documented to have hyperlipidemia, which is known to be a risk factor for cholesterol calculi in the gall bladder. So, if this patient had intermittent and colicky right hypochondrial pain, the possibility of cholelithiasis and/or cholecystitis may also have to be considered.

Dr. Ishii: This patient had pyrexia and hyper-

lipidemia, and was a heavy alcohol drinker. Anyhow, your question was based on the possibility of acute cholecystitis occurring in this patient; good. On laboratory examination, the GOT and GPT levels exceeded 10,000 IU/L. Is it not odd? Fulminant hepatic necrosis may have been present. Do you have anything to add on that, Dr. Yamagishi?

Dr. Yamagishi: Even at the first hospital that the patient had visited, the serum lactate dehydrogenase (LDH) level had been documented to be markedly elevated to 14,900 IU/L. The total bilirubin level had also been determined at Kitasato Institute Hospital; it was very high – the value was 8.25 mg/dl.

Dr. Ishii: On January 26, the patient developed difficulty in even drinking water, and the next day, he was referred to Kitasato Institute Hospital. GOT and GPT are the so-called aminotransferases; when hepatocytes are disrupted, these enzymes leak into the peripheral blood. Mr. Izawa, if we were also to consider the diagnosis of gallstones/cholecystitis at this point, could we have some additional information on other liver function test results as well?

Mr. Izawa: May I ask for the serum levels of alkaline phosphatase (ALP), leucine aminopeptidase (LAP) and γ-glutamyl transpeptidase (γ-GTP)?

Dr. Yamagishi: The γ-GTP level had been determined at the first hospital, and it was 269 IU/L. This level was high, although less markedly so than the serum GOT and GPT. The ALP level was not measured at the first hospital. There was no documentation of the γ-GTP or ALP level at the Kitasato Institute Hospital. The serum LAP had not been measured at either the first hospital or at the Kitasato Institute Hospital.

Dr. Ishii: At present, ALP, γ-GTP and LAP are frequently used as markers of disease of the biliary system. Each of these enzymes reflects one aspect of the functions of the biliary system, and all are important enzyme markers. Their levels were elevated in this patient, but the elevations were less marked than the abnormal elevations of the serum GOT, GPT and LDH, which are reflective of disorders of the hepatocytes themselves, right?

Dr. Yamagishi: That's right.

Dr. Ishii: That is the reason why the patient was admitted to our Keio University Hospital. Dr. Yamagishi, could you please show us the findings on physical examination and the laboratory test results of this patient at admission to our hospital?

Dr. Yamagishi: The patient was slightly obese. The blood pressure was 131/76 mmHg, pulse rate was 93/min and regular, and the body temperature was 38.0°C. There was no anemia, but severe icterus was noted. Xanthoderma was also noted. There were no abnormal findings on examination of the oral cavity. Struma was not present, and there was no cervical lymphadenopathy. No abnormal findings were noted on cardiopulmonary examination. The abdomen was soft and flat. The liver was palpable 2 fingerbreadths below the right costal margin, and was soft to elastic in consistency; it was tender to palpation. The spleen was not palpable. There was no pedal edema. The patient was fully conscious and alert, and there was no consciousness disturbance. Flapping tremor was absent. No abnormalities were found on neurological examination.

Table 1 Laboratory Data

WBC	16200/μl	TP	6.3 g/dl	HA-IgM Ab	(+)
Band	16.0%	ALB	3.2 g/dl	HBs Ag	(−)
Seg	50.0%	ZTT	13.6 KU	HBs Ab	(+)
Lym	23.0%	TTT	7.5 KU	HBe Ag	(−)
Alym	3.0%	TB	7.3 mg/dl	HBe Ab	(−)
Mono	8.0%	DB	6.3 mg/dl	HBc Ab	(+)
Hb	13.8 g/dl	LDH	1640 IU/l	HBV DNA	(−)
Plt	140000/μl	GOT	4130 IU/l	HCV Ab	(−)
Ret	3‰	GPT	5780 IU/l	HCV-RNA	(−)
		GGTP	337 IU/l	CMV-IgG	(+)
		ALP	896 IU/l	CMV-IgM	(−)
PT	21%	ChE	198 IU/l	EB-IgG	(+)
APTT	40.8 sec	BUN	42.7 mg/dl	EB-IgM	(−)
FNG	144 mg/dl	CRTNN	9.1 mg/dl	EBNA	40×
FDP	1497 ng/dl	UA	16.5 mg/dl	HIV Ab	(−)
D-dimer	80.6 μg/ml	NH3	42 μmol/l	HPVB19-IgG	(+)
		CRP	3.77 mg/dl	HPVB19-IgM	(−)
				ANA	(−)

As for the results of the laboratory tests undertaken at admission (Table 1), the erythrocyte sedimentation rate was 7 mm/h, and the white blood cell count (WBC) was markedly elevated to 16,200/μL. The hemoglobin (Hb) was 13.1 g/dl, the platelet (PLT) count was 140,000/μL, and the reticulocyte (Ret) was 3‰. In the coagulation profile, the prothrombin time (PT) was 21.0%, markedly prolonged. The fibrinogen was 144 mg/ml, which was within normal range, and the fibrin degradation products (FDP) level was markedly elevated to 1497 ng/ml.

Dr. Ishii: OK, then, let's go back slightly. Could you please go over the patient's history once more for recapitulation?

Dr. Yamagishi: The patient was a heavy drinker and had been drinking alcohol since he was about 20 years old. He had a few glasses to half a bottle of low-class distilled spirits at least 3–4 times a week. Since he was about 30 years old, he also had whiskey-and-water frequently. Since the age of 32 years, he had had half a bottle of gin, vodka, or other such drinks almost every day. He was an editor of video films, and was single. He often drank while doing his editing work at night. He had led his life without differentiating night from day. He smoked 20 cigarettes a day. Particularly during the holiday period between the end of 1998 and the begin-

ning of 1999, he had drank and eaten without moderation every day, both at parties and while working.

Dr. Ishii: His drinking habit is a very important part of the patient's history, isn't it? Our patient was a heavy drinker, and perhaps also a habitual smoker, since according to the history, he smoked about 20 cigarettes a day, right? He also ate and drank immoderately and intemperately during the year-end holiday between 1998 and 1999, until a few days before and even after the onset of his symptoms. He had had raw fish and uncooked seafood often during this period, right?

We have so far heard about the erythrocyte sedimentation rate, peripheral blood findings and the coagulation profile at the time of his admission. Will you now please also tell us the other biochemical test results on admission?

Dr. Yamagishi: Yes, the serum TP was 6.3 g/dl and ALB was 3.2 g/dl; both were slightly decreased. Remarkably, the serum TB was elevated to 7.3 mg/dl; direct bilirubin level (DB) was predominant, at 6.3 mg/dl. The BUN was 42.7 mg/dl, CRTNN was 9.1 mg/dl, and UA was 16.5 mg/dl. Thus, there was also marked renal dysfunction. In regard to the electrolyte levels, the serum Na was normal, but the serum K was elevated to 6.0 mEq/L. The increased potassium level may have been associated with the renal failure.

Furthermore, the serum LDH was elevated to 1,640 IU/L. As to the subfractions, fractions L3, L4 and L5 were significantly elevated. The serum GOT was 4,130 IU/L, GPT was 5,780 IU/L, ALP was 896 IU/L, and LAP was 218 IU/L. While the latter levels seemed to have improved slightly as compared to the levels recorded at the earlier hospitals, the GOT and GPT were still markedly elevated. The serum γ-GPT and creatine phosphokinase (CPK) were elevated to 337 IU/L and 1,332 IU/L, respectively. There was no documentation at our hospital, but the serum CPK-MB, the fraction derived from the heart, was not elevated.

On admission, the NH_3 level had decreased to 42 μmol/L from the level of 93 μmol/L recorded at the Kitasato Institute Hospital. The serum IgG and IgM levels were elevated to 2,050 mg/dl and 477 mg/dl, respectively.

The serum marker profile of vital hepatitis was as follows: positive for HA-IgMAb, negative for HBsAg, positive for HBsAb, negative for HBeAg, negative for HBeAb, and positive for HBcAb. The patient was negative for HBc (200%). He was also negative for HBc-IgMAb, HBV-DNA, and for both the antibody to and RNA of HCV.

Dr. Ishii: Mr. Izumi, would you have any comments on the data that we have just heard?

Mr. Izumi: Some diseases of the liver may be suspected from the biochemical data. The serological data also indicate that there was probably no active hepatitis B or C infection. Hepatitis A virus (HAV)-IgM was positive, suggesting that the patient probably had active hepatitis A virus infection.

Dr. Ishii: Do you think the liver function abnormalities were related to the HAV infection?

Mr. Izawa: Taking into consideration the serological findings, it is highly likely that the patient had acute viral hepatitis A. However, if only the biochemical findings were considered without taking into consideration the serological data, the elevation of CPK without elevation of the MB isotype suggests that the findings may have been due to the habitual heavy alcohol consumption. There was also renal failure as indicated by the elevated levels of BUN, CRTNN, and K, and when all the findings are considered comprehensively, hepatic disorder due to gallstones and/or cholecystitis may also be considered, as mentioned previously. Other possibilities, i.e., disorders of the biliary tract associated with secondary renal dysfunction may also have to be considered.

Dr. Ishii: So, gallstones/cholecystitis, and renal failure secondary to gallstones/cholecystitis, and alcohol-related disorders may have been related to his condition. Is that right?

Mr. Izawa: The serum CPK level was increased first. It was too high to become a reference, but the GOT was also elevated. High levels of enzymes related to the biliary tract, including ALP, LAP and γ-GTP, were also present. Could you also please let us know the serum triglyceride level, which was not mentioned with the findings?

Dr. Ishii: Yes, the serum triglyceride level. . . .

Dr. Yamagishi: Tryglyceride was not measured on admission. When hyperlipidemia was documented during his earlier medical examinations, the serum total cholesterol was approximately 250 mg/dl. At this time, the serum triglyceride level was approximately 400 or 500 mg/dl. Thus, it may be assumed that the serum triglyceride level was also high on admission.

Dr. Ishii: The serum cholesterol was approximately 250 mg/dl, and the triglyceride was 400–500 mg/dl or over. The normal level of triglyceride ranges from 70–80 to approximately 150 mg/dl. Heavy drinkers often have levels in the range of 300 to 500 mg/dl. A very important morbid condition may be considered from the relationship of CPK to alcohol, in the presence of renal failure. CPK is an enzyme that is present abundantly in the muscle. Elevation of this enzyme level may suggest that disruption of muscle, particularly striated muscle, that has caused leakage of the enzyme into the peripheral blood. So, in heavy drinkers, what do you think has happened when the serum CPK level is elevated?

Mr. Izawa: Myositis may be caused by alcohol consumption. The associated rhabdomyolysis induces re-

lease of the MB fraction of CPK, which causes proximal tubular dysfunction in the kidney. That could have happened.

Dr. Ishii: I see. Rhabdomyolysis is sometimes associated with alcoholism. Particularly, it occurs in alcoholics, often causing renal failure. Oliguria and anuria may also occur. In some cases, the serum CPK level may be elevated from 1,000 to 2,000 or 3,000 IU/L. This morbid condition is very uncommon, but as Mr. Izawa thinks, it must be kept at the back of the mind for the time being.

Mr. Ikegami (6th-year student): I also think that the influence of alcohol should never be ignored. Hepatitis A is the most plausible diagnosis based on the serological test findings. In particular, at least the other viral hepatitis can be ruled out from the serological findings. In cases of hepatitis with elevated serum CRP level, hepatitis A would be suspected first among the viral hepatitis. The levels in the present patient were characteristic of hepatitis A; thus, hepatitis A would be the most plausible diagnosis.

Dr. Ishii: Yes, you have a very good point. Hepatitis with elevated serum CRP level is most frequently seen in cases of hepatitis A.

Can you tell us what other possible diseases should be kept in mind, Mr. Igarashi?

Mr. Igarashi: The count of atypical lymphocytes in the peripheral blood was 3%, suggesting that infectious mononucleosis is a possibility. However, in this patient, this is unlikely because of the absence of peripheral lymphadenopathy. Still, hepatic dysfunction was associated with hepatosplenomegaly, in addition to lymphocytosis; therefore, infectious mononucleosis may have to be considered as a possibility.

Dr. Ishii: Infectious mononucleosis? The patient did not have lymphadenopathy – so what do you think of that?

Dr. Yamagishi: No, the patient did not have lymphadenopathy.

Dr. Ishii: Lymphadenopathy is an important finding. Although it is possible to find that in physical examination, CT or ultrasonography of the abdomen may reveal enlarged para-aortic lymph nodes. Therefore, it should be considered as one of the possible diagnoses.

Mr. Abe, do you have any comments?

Mr. Abe (6th-year student): Various medicines had been prescribed to the patient for the treatment of cold-like symptoms. Therefore, drug-induced hepatitis may also have to be considered.

Dr. Ishii: Right. During the 2–3 weeks between early January and January 27, various medicines had been administered to the patient. Thus, drug-induced liver disease may indeed have to be considered as a possibility. Do you have any comments about other possible morbid conditions?

Mr. Izumi: I have a question. Was the patient's fundus examined at admission for papilledema?

Dr. Yamagishi: Papilledema was not examined.

Mr. Izumi: If we consider infectious mononucleosis as a possibility as mentioned earlier, what were the antibody titers to Epstein-Barr (EB) virus in the serum? What other tests were performed to substantiate or rule out the diagnosis? Could you please let us know?

Dr. Ishii: Dr. Kikuchi of the Department of Laboratory Medicine, would you please answer that question?

Dr. Kikuchi (Department of Laboratory Medicine): EBV antibody-IgG and antibody-IgM examined in this patient were the antibodies response to the various antigens of EB virus. They are not antibodies to specific antigens of EBV, such as viral capsid antigen (VCA), early antigen (EA) and Epstein-Barr virus nuclear antigen (EBNA). Basically, in EBV infection disease, IgM is elevated in the initial stages, and later, IgG, is elevated. When the latter alone is elevated, it indicates mainly past infection. In the present patient, EBNA was examined separately. EBV-IgG and -IgM antibodies, which are the tests performed generally at our hospital at present, are not antibodies against specific EBV antigens as I just commented.

Mr. Izumi: Autoimmune hepatitis should also be considered in the differential diagnosis.

Dr. Ishii: Why do you think so?

Mr. Izumi: There is no specific evidence, but I thought it may be necessary to consider autoimmune hepatitis, because the patient after all had hepatitis.

Dr. Ishii: Before considering autoimmune hepatitis, let us discuss the immunoglobulins levels in the patient, as it is a very important issue. In this case, the overall Ig level, including IgG, IgA and IgM, was found to be approximately 2,800 mg/dl on admission. Thus, there was probably a polyclonal elevation of the γ-globulin level. The test for antinuclear antibody was negative, which goes against the consideration of autoimmune hepatitis, nevertheless, this condition may have to be kept in mind as a differential diagnosis.

Bone marrow aspiration was performed in this patient at admission, wasn't it? Would you please tell us about that? Also, let us see the findings of CT and other imaging studies.

Dr. Yamagishi: Because of marked renal dysfunction, contrast-enhanced CT was not performed.

Dr. Ishii: Iodine was probably not used because of the presence of renal failure?

Dr. Yamagishi: That's correct. The liver was swollen with tension, showing a considerably lower density as compared to the spleen. The spleen was also swollen. There was no ascites. Severe renal dysfunction was present on laboratory data, but no renal atrophy was observed.

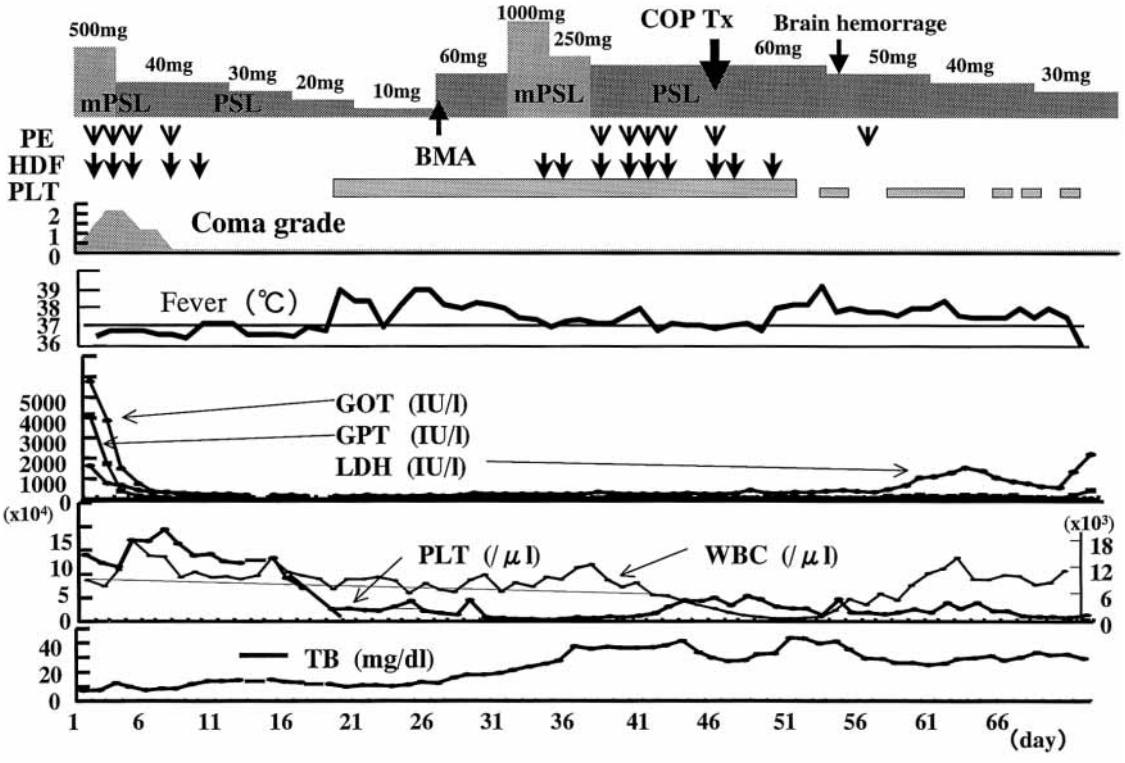

Fig. 1 Outline of the clinical coarse. PE: plasma exchange, HDF: hemodiafiltration.

Dr. Ishii: Dr. Yamagishi said now that the liver showed uniformly low density, but how do you see this? The density must be seen in contrast with another organ. Certainly the liver is low density in this case. It is important to compare its density with the density of normal liver. Usually, the spleen and the liver show isodensity. In this case, the liver is distinctly of lower density than that of the spleen. In addition, the liver showed diffusely low density.

When low density is diffusely present as compared to the density of the spleen, what should be considered first, I wonder. If a local space-occupying lesion shows low density, various possibilities can be considered. In the case of diffuse low density, however, the most important condition that must be considered is alcoholic liver disease. Fatty liver may also be considered, which is also commonly seen in alcohol liver disease. The diffuse low density is caused by fatty infiltration.

Significant swelling of the liver and low density are characteristic of a fatty liver.

Dr. Yamagishi: This is a supplementary finding, but the gallbladder is also considerably contracted, with thickening of the wall.

Dr. Ishii: The gallbladder can be visualized and shows generalized contraction. The gallbladder is known to contract after meals. So, how would one judge the contraction in this case, Dr. Yamagishi?

Dr. Yamagishi: A contracted gallbladder with thickening of the wall is quite frequently seen in acute phase of severe hepatic disorders.

Let me now describe to you the course of the patient after admission (Fig. 1). The patient was diagnosed to have severe acute hepatitis at the Kitasato Institute Hospital, and acute renal failure was diagnosed to be present, in addition, at our hospital. From the day of admission, marked prolongation of PT was observed. Administration of FFP was started for supplementation of coagulation factors, and hemodialysis was started for acute renal failure. Steroid pulse therapy was started with 500 mg of methylprednisolone (mPSL) for the treatment of the liver disorder. On the day after admission, the patient developed Grade II hepatic encephalopathy with flapping tremor. At this point, he was diagnosed to have acute fulminant hepatitis according to the diagnostic criteria established at the Inuyama Symposium, and plasma exchange (PE) and hemodiafiltration (HDF) were started.

On hospital day 6, the serum GOT and GPT levels and the PT showed marked improvement to 63 IU/L, 348 IU/L and 71%, respectively, in response presumably to the steroid administration, PE and HDF. The encephalopathy improved and the PE and HDF were stopped. However, hemodialysis was continued for the renal dysfunction. For 3–4 days after admission, the

patient had anuria, but thereafter diuresis occurred, and the renal function also tended to gradually improve. While the dose of the steroid was being tapered, however, the patient developed some other symptoms; from hospital day 18, when the dose of PSL was tapered to 20 mg, pyrexia of over 39.00°C, marked elevation of the serum CRP, and thrombocytopenia developed, and the PLT count decreased to under 10,000/μL, despite PLT transfusion every day. On hospital day 24, bone marrow aspiration was done. This revealed numerous activated macrophages with phagocytosed hemocytes with vacuoles. Taking into consideration this finding along with the clinical course, the patient was diagnosed to have hemophagocytic syndrome (HPS).

From hospital day 28, steroid pulse therapy with 1,000 mg mPSL and administration of gabexate mesilate (FOY) were started. With this treatment, the pyrexia tended to resolve, the temperature reduced to 37.00–38.00°C, the serum CRP level decreased slightly. A bone marrow aspiration has done again on hospital day 36, however, still revealed macrophages with phagocytosed activated hemocytes. In consultation with hematological physician, chemotherapy with Cyclophosphamide, Vincristine, and Prednisolone (COP therapy) was started from hospital day 36.

Subsequently, the PLT count improved to over 30,000/μL, and the frequency of PLT transfusions could be reduced. The total bilirubin, which had risen to 40 mg/dl, decreased to under 30 mg/dl. However, granulocytopenia, which may be considered to be a side effect of chemotherapy, developed, and this could be corrected to some extent by the administration of G-CSF. The general condition of the patient seemed to show some gradual improvement, but on hospital day 48, the patient developed a cerebral hemorrhage, and went into respiratory arrest. Mechanical ventilation was initiated, and glyceol was administered for cerebral edema. However, the patient did not respond to the treatment, and died on hospital day 66.

Dr. Ishii: We just heard the patient's clinical course after his admission to the hospital until his death. After admission, various examinations were conducted. It was stated that while tests were being performed to confirm the diagnosis, the patient developed acute fulminant hepatitis. You students also often use the term ''fulminant hepatitis'', but what is acute fulminant hepatitis? Mr. Izumi, what are your comments on the diagnosis of acute fulminant hepatitis?

Mr. Izumi: The criteria established at the Inuyama Symposium include the following in the category of hepatitis: fulminant hepatitis is characterized by having Grade II or more severe encephalopathy and severe liver dysfunction occurring within 8 weeks of the appearance of symptoms, with a prothrombin time of 40% or less. On the basis of these criteria, this patient's condition could be diagnosed as fulminant hepatitis. Within 10 days of the appearance of symptoms, encephalopathy occurred, reflecting the acuteness of the condition. Thus, the patient was diagnosed to have acute type fulminant hepatitis.

Dr. Ishii: I see. Dr. Saito, could you comment on the diagnosis of fulminant hepatitis in this case?

Dr. Saito: The diagnostic criteria for fulminant hepatitis which were just mentioned by student Izumi are correct; they were established at the Inuyama Symposium. But I must say that the categorization of acute hepatic failure is somehow different between Japan and other countries. Therefore, I am going to talk about the Japanese consensus of fulminant hepatic failure. Fulminant hepatitis is included as a category of acute hepatic failure, in which the function of the liver as an organ becomes severely impaired because of rapid disruption of a large number of hepatocytes. There are acute and subacute types of fulminant hepatitis; in the acute type, disturbance of consciousness appears within 10 days of the onset of symptoms, and in the subacute type, disturbance of consciousness develops on or after the 11th day of the occurrence of symptoms. In general, the subacute type is more severe. The life of a patient with the subacute type can rarely be saved; the survival rate in cases with the acute type is approximately 50–60% and that of cases with the subacute type is currently estimated to be 30% (20% according to previous data). Acute hepatic failure is also not infrequently associated with hepatitis A.

Dr. Ishii: Thank you, Dr. Saito.

Then, we would like to ask Dr. Yamagishi, the physician-in-charge of the patient, about the survival rate of cases of acute fulminant hepatitis, the eventual diagnosis in this patient, and the treatment for the condition.

Dr. Yamagishi: There was clear evidence that the patient had acute hepatitis A. Even in cases with acute hepatitis A, elevation of the GOT and GPT to over 10,000 IU/L is not considered to be common. The heavy alcohol consumption was considered to have had much influence on the clinical condition and laboratory abnormalities in the present case.

With regard to renal failure, nephropathy is well known to be associated with severe acute hepatitis A. Although the cause still remains unknown, many cases develop acute tubular necrosis. There is a hypothesis that immune complexes precipitate in the kidney to lead to renal failure. Other factors, including the influence of alcohol or drugs, because antipyretics, particularly NSAIDs, and antibiotics, had been used in high doses, may also have been related to the development of renal dysfunction in this patient.

In other words, acute hepatitis A was present as the underlying disease, and the condition became severe

due to the additional influence of alcohol in this case. Drugs also probably influenced the underlying disease. The condition in the patient worsened, with the development of fulminant hepatitis, encephalopathy and renal failure in this patient.

Dr. Ishii: We understand that acute hepatitis A was diagnosed based on the clinical findings, but there is another problem. We must also consider the possibility of a very important complication or disease secondary to the hepatitis, based on the manifestation of marked pyrexia and the changes in the hemopoietic system. In particular, marked thrombocytopenia started to be seen from hospital day 18 (middle of February). Such a complication in association with hepatitis A is extremely rare. So, what was the cause of this? We presented the various hematological findings and discussed the case with Dr. Okamoto. We asked him that under the circumstances, what had actually occurred in this patient? The data will be discussed by Dr. Okamoto, but before that, Dr. Yamagishi, will you please tell us about the bone marrow aspiration?

Dr. Yamagishi: Thrombocytopenia was marked and the PLT count did not increase despite PLT transfusion every day. In order to determine the cause of the decreased PLT count and the treatment strategy, we consulted with hematological physician at our hospital, and decided to perform a bone marrow aspiration.

Dr. Ishii: Dr. Okamoto, will you please explain the condition of the patient, as well as the results of the bone marrow aspiration?

Dr. Okamoto (Internal Medicine): When we saw this patient with severe thrombocytopenia, we assessed whether the patient had depressed hemopoiesis, or conditions in which blood cells were rapidly consumed or destroyed. The findings of severe thrombocytopenia outpropotional to anemia and leukopenia, a shift of granulocytes to the left, and increased RET counts support the latter possibility. Bone marrow biopsy was performed to confirm this, and revealed hypercellular marrow with marked hemophagocytosis (Fig. 2).

I will first give a general overview of the condition called HPS (hemophagocytic syndrome), and then discuss the possible causes of HPS in this patient.

This slide shows bone a marrow smear of this patient. Bone marrow is normocellular with normal erythroid and myeloid differentiations. A macrophage is observed in the center, and you can see the macrophage eating and digesting red cells and platelets (Fig. 3).

This is a bone marrow smear of another patient with lymphoma. This patient also had severe HPS. You can see platelets, granulocytes, and erythroblast being phagocytosed and digested by a macrophage.

When a bone marrow smear is prepared, macrophages and RBCs may overlap each other, and occasionally result in an image like phagocytosis. However, if you check smears carefully, you can see the clear zone around phagocytosed cells in the cytoplasm. This is a typical finding of endocytosis.

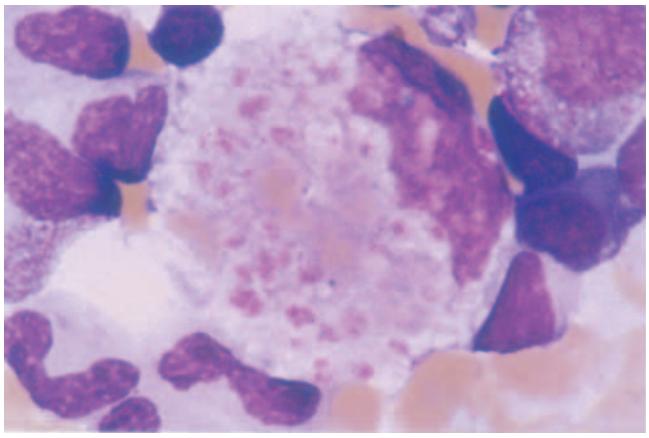

Fig. 2 Bone marrow macrophage from this patient. The macrophage shows platelet phagocytosis.

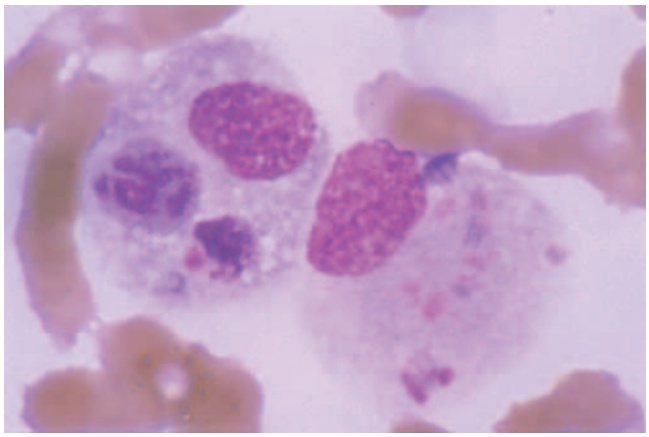

Fig. 3 Bone marrow macrophages from a patient with lymphoma. These macrophages show platelet phagocytosis, band neutrophil and erythro-phagocytosis.

HPS is a clinical entity characterized by activation and proliferation of histiocytes and macrophages. As a result, mature blood cells are phagocytosed and digested by these activated cells in the bone marrow. Phagocytosis does not necessarily occur only in the bone marrow; it may also occur in the liver and the spleen. In order to diagnose this syndrome bone marrow aspiration is the most valuable tool. If phagocytosis in the bone marrow is not distinct, the liver and the spleen may also be biopsied, but the yields are comparatively low.

Clinical features of HPS are largely attributable to the cytokine storm, i.e., a condition in which a large amount of cytokines is produced. It has been believed

Table 2 Classification of Hemophagocytic Syndrome in Adults (N = 52)

Underlying disease	No. of cases
Lymphoma-associated hemophagocytic syndrome (LAHS)	
T/natural killer lymphoma	12
B lymphoma	12
T/B unknown	2
Virus-associated hemophagocytic syndrome (VAHS)	
Epstein-Barr virus	4
Measles	1
Parainfluenza	1
Hepatitis A	1
Not identified	10
Bacteria-associated hemophagocytic syndrome (BAHS) and fungal infections	
Mycobacterium tuberculosis infection	2
Staphylococcus aureus infection	1
Pseudomonas aeruginosa infection	1
Corynebacteria infection	1
Candida albicans infection	1
Autoimmune-associated hemophagocytic syndrome (AAHS)	
Systemic lupus erythematosus	3

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that macrophages and histiocytes are activated by the ''cytokine storm'' in this condition. The clinical findings include high fever, hepatomegaly, splenomegaly, cytopenia due to phagocytosis of blood cells. Laboratory findings showed elevation of LDH due to destruction of blood cells and high level of CRP, soluble-interleukin-2 receptor (sIL)-2R, triglyceride and ferritin, which are attributable to the increased cytokine levels. Liver dysfunction and abnormal coagulation profiles are also observed (Table 2).

What are the underlying diseases associated with HPS? As mentioned by Prof. Ishii, HPS is rarely associated with hepatitis A, according to a nationwide survey of HPS in adults by Akita University School of Medicine. The most common underlying disease associated with HPS was lymphoma, followed by viral infections (so-called virus-associated hemophagocytic syndrome; VAHS). It has been reported that VAHS may be associated with EB virus, measles, parainfluenza, hepatitis A, parvovirus, herpes simplex virus, herpes zoster virus and adenovirus infections. Ten cases associated with possible viral infection, in which causative viruses could not be identified, have been reported. Severe bacterial infection or fungal infection, just like viral infection, have also been reported to be associated with HPS. Similarly, HPS has also been reported in association with severe autoimmune diseases.

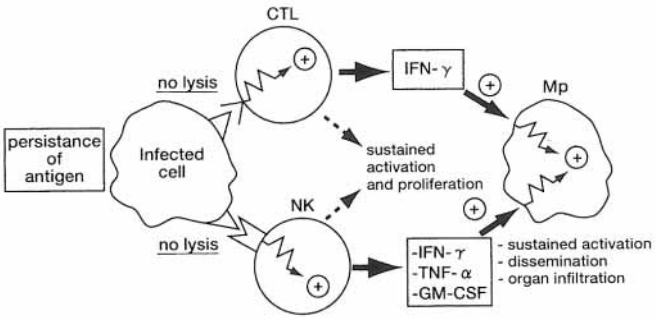

Fig. 4 Schematic representation of the cytolytic effector cell defect in HLH. (Reproduce from Arico M, *et al*: Br J Hematol 2001; 114: 761–769, Copyright © (2002), requesting permission from Blackwell Publishing)

On the other hand, many familial cases have been reported in children. That is called familial hemophagocytic lymphohistiocytosis (FHL). The incidence of HPS related to EBV virus infection seems to be higher in children (Fig. 4).

This is my last slide, showing the mechanism of hemophagocytic lymphohistiocytosis in children. Here you can see a virus-infected cell, and cytotoxic T lymphocyte (CTL), natural killer (NK) cell attacking the infected cell. When NK cells attack infected cells, they often secrete perforin to make holes at the cell surface, and inject a substance called granzyme into the holes, which induces apoptosis of the cell. In pediatric patients with FHL, the ability of NK cells to produce perforin is markedly decreased or deficient. Therefore, while NK cells are activated, infected cells are not killed. As a result, cytokines are constantly produced and macrophages continue to be activated, and result in HPS. Therefore, not macrophages (MP), but NK cells and T cells are responsible for the occurrence of HPS. In lymphoma, there is a possibility that lymphoma cells themselves also produce cytokines.

In this patient, NK cells or CTL had some defects, and the infected cells could not be killed because of the healing process, as a result, the ''cytokine storm'' may have progressed. It is also possible that T cells or NK cells show clonal proliferation in this condition, while the infection settled. The possibility of another viral infection, not hepatitis A, having occurred during the healing process of hepatitis A cannot be ruled out. This viral infection may have been the cause of HPS in this patient.

As for the treatment of HPS, it is most important to suppress the ''cytokine storm''. Steroids and cyclosporine should be administered to suppress cytokine production from T cells and/or NK cells. When these therapeutic procedures fail, hemopoietic stem cell

transplantation may be considered to eliminate the proliferating T cells or NK cells completely. There have been a limited number of reports of stem cell transplantation in HPS. Liver transplantation has also been performed, in addition to hemopoietic stem cell transplantation in some patients.

In conclusion, hepatitis A may have triggered the HPS in this patient, and subsequently the ''cytokine storm'' persisted, and contributed to the fatal course. What I want to know is whether another infection such as EBV infection was present, whether the hepatitis A infection was completely resolved at the time of occurrence of HPS, and finally, whether the HPS in this patient was associated with lymphoma, although this is unlikely.

Dr. Ishii: We understand that very well; any questions?

Mr. Tamura (5th-year student): A doctor mentioned previously that it was difficult to make a diagnosis based on a correlation among hepatitis, the patient's symptoms, and the laboratory test values. In this patient, the ferritin level was considered to be very abnormal. While the accurate condition was not known because the RBC count was not monitored, in general, the ferritin level seemed to be elevated. What are the possible reasons for elevation of the ferritin levels in cases of hepatitis?

Dr. Saito: Usually, the ferritin level is not elevated in cases of viral hepatitis. In cases of liver transplantation, that are always due to chronic and acute liver diseases in adult, VAHS or hemophagocytosis happens to be complicated. If the activity of VAHS or hemophagocytosis is severe, the prognosis of the patient will be determined by the severity of the hematological diseases, even if the liver is successfully transplanted. We must decide whether or not the transplantation should be performed. In such cases, the phagocytotic activity may be judged from serum level of ferritin and IL-2R.

Mr. Tamura: In the familial type mentioned previously, it was said that the condition is caused by weakening of the functions of CTLs and so on, right? Then, is this not manifested by any other signs, such as increased susceptibility to infections from birth?

Dr. Okamoto: It's a good question. Pediatric patients with FHL do not often live to grow into adults. So, in most adult patients, HPS is associated with lymphoma or viral infection. However, HPS in association with hepatitis A is rare, even though the hepatitis is severe. It is plausible to speculate that abnormalities in the immune system, which are being increasingly clarified in pediatric patients, may also exist in adults. But this is a speculation, and has not been demonstrated.

Mr. Izumi: This patient had acute fulminant hepatitis and should have had a better prognosis than cases with subacute fulminant hepatitis. Did you consider liver transplantation in this patient?

Dr. Ishii: Yes, I was going to ask Dr. Saito to talk later about liver transplantation. But before that, let me ask Dr. Okamoto about a matter related to his field; the various data of cytokines in this patient were collected at the start of pulse therapy. Dr. Okamoto, in relation to your previous interpretation, will you give some comment about this?

Dr. Okamoto: When the sIL-2R level was high, hepatitis seemed clinically controlled. Therefore, the ''cytokine storm'' may have been caused by other factors such as activation of the immune system. The high IL-6 level also suggests that T cells were activated. The TNF-γ level should also have been elevated, however, TNF-α and interferon are easily inactivated unless the levels are measured immediately after sampling. Therefore, the fact that these levels were not elevated does not necessarily indicate the absence of the ''cytokine storm''. The IL-6 and IL-2R levels were high. These findings would be adequate to assume an excessive activation of T cells and NK cells.

Dr. Ishii: We looked at one section of the ''cytokine storm''. As for Dr. Okamoto's comment, do you have any opinion from the clinical aspect, Dr. Yamagishi?

Dr. Yamagishi: The Hb level of the patient was determined to be about 9.5 g/dl on the day of bone marrow aspiration, and 13.1 g/dl at admission. Thus, the Hb level also decreased along with the platelet count. TNF-α was determined slightly later in samples of serum stored frozen. The TNF-α level was determined again on hospital day 40. On this occasion, it was determined immediately after the blood sample was obtained, and was found to have elevated to over 20 pg/ml.

Dr. Ishii: Living related liver transplantation has been performed at our Keio University Hospital for 4–5 years, at least in 55 cases so far. Living related liver transplantation has recently also been actively performed for cases of fulminant hepatic failure. Dr. Saito, could you please let us know more on this subject, including its current status and its future application.

Dr. Saito: Let me tell you about hepatic transplantation for fulminant hepatitis in Japan. The criteria for hepatic transplantation in acute hepatic failure have been determined for subjects of cadaver liver transplantation. The first process of assessment for transplantation in such cases considers the following 5 items: (1) The age at the time of occurrence of encephalopathy, 45 years or over; (2) the number of the days before the occurrence of encephalopathy, 11 days or more, i.e., whether or not the hepatitis is subacute; (3) prothrombin time (PT), 10% or less; (4) total bilirubin, 18 mg/dl or more; and (5) the ratio of DB to total bilirubin, 0.67 or less. When 2 of the 5 items are satisfied, death is predicted and liver hepatic transplantation is considered.

For 5 days, intensive medical treatment is carried out. When the following 2 items are met at this time point, the patient is excluded from consideration for transplantation: (1) Prothrombin time (PT) improved to 50% or more, and (2) encephalopathy improved to Grade I or milder. When either of the items is not satisfied, the patient may still be considered for transplantation.

Cadaver liver transplantation has very rarely been performed in Japan. Living-related transplantation also adheres to a set of criteria. In our Keio University Hospital, liver transplantation has been performed on 11 patients with acute hepatic failure so far. Unfortunately, 2 of them died thereafter, but 9 patients survived. All of these 9 patients were judged to be dead both on day one and five, but their lives were saved by the transplantation. Thus, since transplantation has become possible and also our medical treatment has been much improved, the survival rate in cases of acute hepatic failure has rapidly risen with or without liver transplantation. This is the present situation.

Dr. Yamagishi: EB virus marker was examined for again after the diagnosis of HPS, but similar negative data were obtained. However, EBV-DNA was not examined.

There was no evidence of active cytomegalovirus infection, either. Parvovirus B19 was also examined, but the test was negative.

The acute hepatitis A was considered to be resolving, but HPS occurred as the dose of steroid was being tapered, suggesting the possibility of the HPS having been masked by the steroid administration.

Dr. Ishii: We were told that HPS appeared in the setting of acute fulminant hepatitis. If there are any questions or comments about the causal relationships up to this point, we would like to discuss that.

Mr. Izumi: As previously explained by Dr. Okamoto, was this patient considered for peripheral blood stem cell transplantation (PBSCT) and bone marrow transplantation?

Dr. Yamagishi: After the start of chemotherapy, side effects including leukocytopenia were observed. However, this resolved to some extent with treatment, and the PLT and coagulation profile also improved, but the patient developed cerebral hemorrhage before transplantation could be considered.

Mr. Ikegami: After HPS occurred in this patient, COP therapy was selected. The treatment could have included other drugs, for example, cyclosporin A, etc. This patient had fulminant hepatitis A as an underlying disease, the severity of which was influenced by the habitual alcohol drinking. Other body functions may also have been impaired by the alcohol drinking. I would like to know whether there were some alternative choices to COP therapy.

Table 3 Summary of Anatomical and Histopathological Findings

1. Hemophagocytic syndrome after chemotherapy
   - Proliferation of macrophages and hemophagocytosis, severe
     - a) Liver (2400 g) with severe bile stasis
     - b) Spleen (1070 g)
     - c) Bone marrow
   - Related lesions:
     - Pancytopenia
     - Hyperplastic bone marrow, mild
   - Therapies:
     - Steroid pulse (mPSL)
     - Chemotherapy (COP therapy: Endoxan 900 mg + Oncovin 0.75 mg + Predonine 60 mg, 1 cool)
2. [Fulminant hepatitis] (2400 g)
   - Anti-human hepatitis virus type A antibody: (+)
3. Systemic aspergillosis
   - a) Bilateral severe pneumonia with abscess formation (450, 580 g)
   - b) Bilateral renal abscesses (250, 250 g)
   - c) Endocarditis with vegetation (380 g)
   - d) Thyroidal abscesses, right lobe (18.8 g)
   - e) Spleenic abscesses (1070 g)
4. Icteric kidney (250, 250 g)
5. [Brain hemorrhage]

Dr. Ishii: Dr. Okamoto, could you please explain the choice of the therapeutic strategy, including the reason for choosing COP therapy.

Dr. Okamoto: As described previously, early judgment of the possibility of self-limiting healing is the most important before you start treatment. If you think that the self-limiting healing is unlikely, hemopoietic stem cell transplantation with any kind of graft should be positively considered. While preparing for transplantation, treatments to suppress hemophagocytic activity and the release of cytokines from activated T cells should be provided. The treatment of choice includes the administration of steroids with or without chemotherapeutic agents such as VP-16, cyclophosphamide and vincristine. Cyclosporine should also be given to suppress the activity of T cells.

Dr. Ishii: Now let us discuss the autopsy findings.

Dr. Kodama (Pathology): I would like to present the pathological findings. The autopsy findings are summarized in Table 1. Bone marrow showed mild hypercellularity and prominent proliferation of macrophages, which were identified by immunostaining with anti-CD68 antibody (Fig. 5A). Many of the macrophages had a large volume of cytoplasm which contained erythrocytes, partially-digested myelocytes and thrombocytes (Fig. 5B and 5C), indicating that these macrophages were hemophagocytic. Macroscopically, the liver appeared swollen, but there was no massive hepatic necrosis or fibrosis (Fig. 6A). The weight was 2,400 g and the color indicated intrahepatic bile stasis. Microscopically, numerous macrophages, most of which were

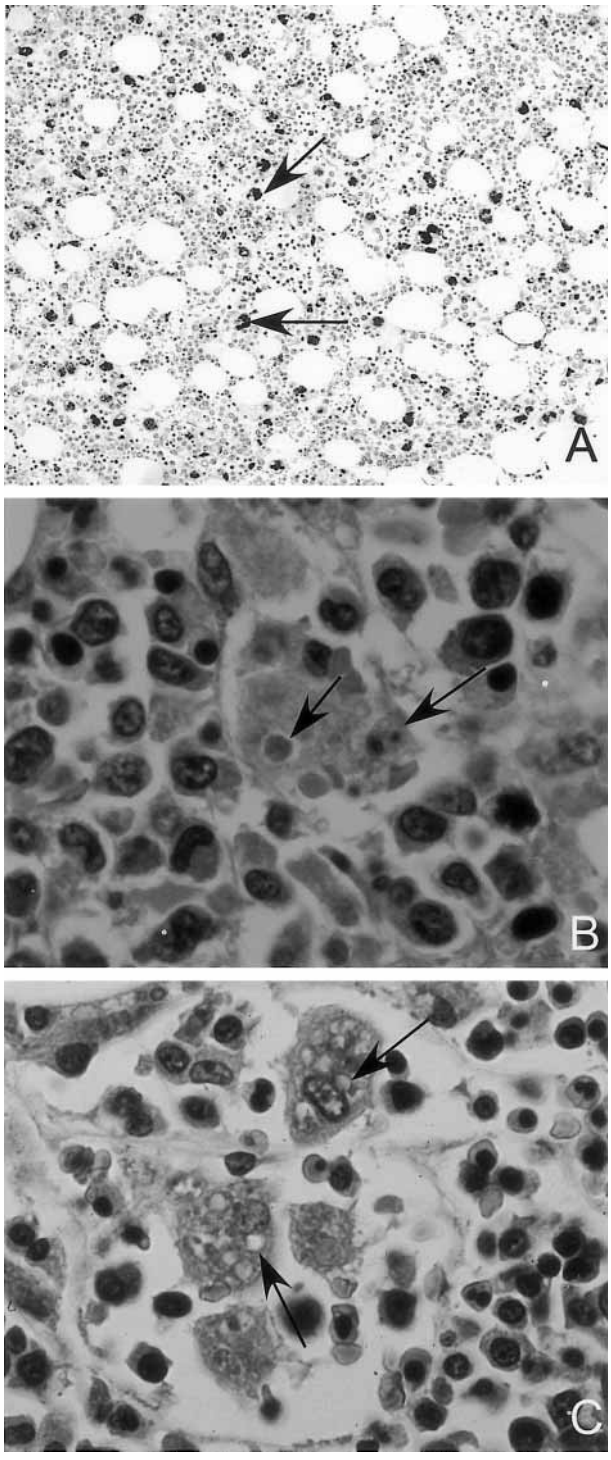

Fig. 5 Microscopic findings of the vertebral bone marrow. **A**, Immunostaining with anti-CD68 antibody. Note numerous macrophages positively immunostained (allows) in the hypercellular bone marrow. **B** and **C**, Macrophages (allows) containing erythrocytes, blood cells and vacuoles. (×400)

hemophagocytic, were present in the enlarged sinusoids (Fig. 6B). At the portal areas, there was severe bile stasis (Fig. 6C). Necrotic changes and inflammatory

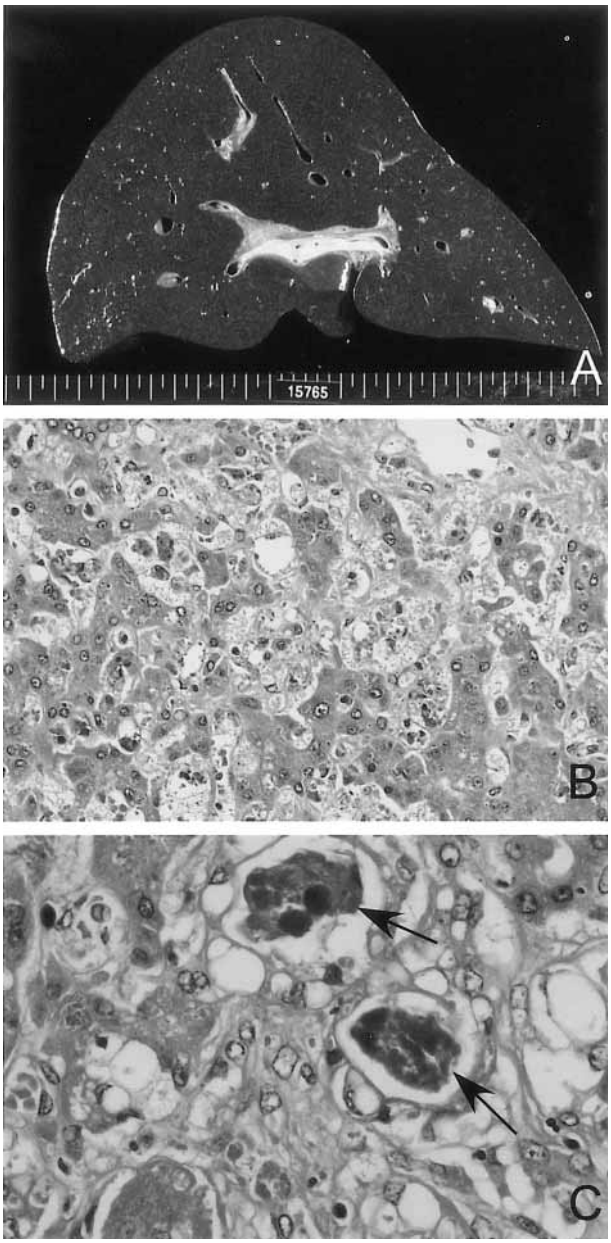

Fig. 6 **A**, Macroscopic appearance of the liver. Liver shows swelling, but no necrosis or fibrosis. **B** and **C**, Microscopic findings. Enlarged sinusoids are full of macrophages, which englobed blood cells (B). At the portal areas, bile stasis is seen (allows). (×400)

cell infiltration were seldom seen in the liver and fibrosis was not observed by Elastica van Gieson staining. Based on the pathological findings at autopsy, the fulminant hepatitis diagnosed during the patient's clinical course was believed to have been cured. Thus, the pathological diagnosis of the liver was hemophagocytic syndrome. The spleen was huge, weighing 1,020 g, about 10-fold larger than a normal spleen. There were many macrophages which had englobed blood cells. The bilateral lungs showed severe pneumonia with

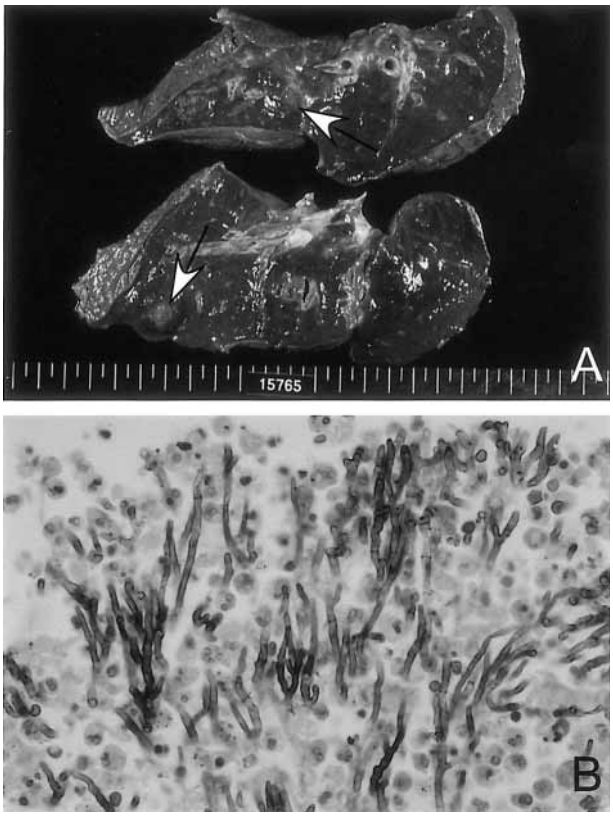

Fig. 7 **A**, Macroscopic appearance of the lung. The lungs show severe pneumonia with various-sized abscesses (allows). **B**, Grocott's staining of the lung. Note that there are a lot of mycelia of *Aspergillus*, which branch at acute angles (40 degree). (×400)

various-sized abscesses (Fig. 7A). Multiple abscesses were also found in the kidneys, thyroid and spleen. Microscopically, all of the abscesses had necrosis, prominent neutrophil infiltrations and mycelia of fungus, which were stained by Grocott's staining (Fig. 7B). The mycelia branched at acute angles (~40°), which is specific for *Aspergillus*. The heart showed endocarditis with small mural vegetation in the left ventricle, and the base of the vegetation had abscesses with mycelia of *Aspergillus*. Thus, the patient was considered to have suffered from sepsis.

Hemophagocytic syndrome is commonly associated with viral infections including Epstein-Barr virus, human hepatitis virus types B and C, and also with carcinomas and malignant lymphomas. However, hemophagocytic syndrome associated with hepatitis virus type A infection is rather rare, and only a few cases have been so far reported. In the present case, we could exclude the possible association of Epstein-Barr virus infection, malignant tumors and malignant lymphoma.

In summary, we have presented a case of hemophagocytic syndrome, which emerged during the treatment for fulminant hepatitis caused by hepatitis virus type A infection. Although the fulminant hepatitis was almost cured, immunosuppressive therapy for hemophagocytic syndrome induced *Aspergillus* infection and finally the patient died of multiple organ failure due to sepsis.

Dr. Ishii: Thank you for your comments, Dr. Kodama.

The patient had acute hepatitis A, which became fulminant. However, fulminant hepatitis itself could be controlled for the time being. However, HPS appeared, didn't it?

Dr. Yamagishi: Yes, it did.

Dr. Ishii: Usually, it is impossible for autopsied liver of fulminant hepatitis to weigh as much as 2,400 g. Fulminant hepatitis usually shows acute liver atrophy. So in fulminant hepatitis patients we have experienced, who were subjected to autopsy, the liver weighed 500 g or 700 g. This fact indicates massive hepatic necrosis. When observing the pathological findings, various changes replacing the findings can be observed with attention. Dr. Saito and Dr. Okamoto, please give some comments from your respective standpoints about the aforementioned pathological findings.

Dr. Okamoto: We have treated 6 patients with HPS, but only one patient survived after the treatment. What we have learned during the treatment is that controlling of infection is important. In patients with HPS it is difficult to confirm the presence of infection, because one of the symptoms of HPS is high fever, furthermore, the patients are usually pancytopenic, and receive high-dose steroids as a part of treatment. Those make the patients more susceptible to infections. Therefore, much attention must be constantly paid to infection. This patient had *Aspergillus* pneumonia. In the patients whom we treated before, immunosuppressants at a high dose have been used, and eventually about half of them died with fungal or *Pneumocystis* infections.

Since this patient had pneumonia in the lower lobe, early detection may have been difficult by chest X-ray. However, it has become possible to detect fungal infection earlier by monitoring β-glucan, *Aspergillus* antigen, or PCR. Recently, newer antifungal agents such as voriconazole and liposomal amphotericin B have become commercially available, and the results of the treatment of *Aspergillus* infection have been markedly improved. If this patient had overcome the infection, he might have recovered.

Dr. Saito: After having this patient, the treatment environment for patients with fulminant hepatitis has been changed to an aseptic room. When listening to the pathological findings today, I am really impressed that the liver is an organ with the very high ability to regenerate. The hepatic encephalopathy was very severe, the bilirubin level was elevated, and prothrombin time (PT) was decreased. In other words, hepatocytic necrosis, which was so massive that would induce hepatic

Table 4 HPS Related Hepatitis Virus A

Pt No.	Age	Sex	Fever °C	Hepato-splenomegary	GOT IU/l	GPT IU/l	LDH IU/l	TB mg/dl	HA-IgM	Ferritin ng/ml	Plt/μl
1	20	F	39	+	3270	1880	5480	20.0	+	2287	49000
2	23	M	39.5	+	355	367		31	+		10000
3	40	M	+	+	2250	2000	3482	1.7	+	4652	37000
our case	36	M	40	+	4130	5780	1640	43	+	4080	<10000

Pt No.	Therapy	Underlying disease	Outcome
1	Steroid, VP-16	Still disease	Died (liver failure, DIC)
2	Steroid	HCV	Died (GI bleeding, DIC)
3	None	None	Survived
our case	COP Tx	None	Died (Brain hemorrage)

1. Journal of Medical Virology, 1993.
2. The American Journal of Gastroenterology, 1995.
3. The American Journal of Gastroenterology, 1998.

failure, was present, but in spite of this, the liver was restored to such a level within 2 months. I thought this demonstrated that hepatocytes of the necrotic site are regenerated along with absorption of fibrosis.

Dr. Ishii: Thank you for your comments, Dr. Saito.

In addition, the long history of heavy alcohol drinking cannot be ignored in this patient. With continuous heavy drinking of a large quantity of alcohol for so long the immunological functions may be impaired, even though this patient was still only in his 30's. Alcohol also greatly suppresses cellular immunity, in the sense that the reticuloendothelial function is disturbed. In this background, the patient also had infection with hepatitis A virus.

Cases of HPS associated with hepatitis A collected by Dr. Yamagishi.

Dr. Yamagishi: As for reported cases related to HAV, a review of literature revealed 3 patients reported in the world by the year 2000 (Table 4). However, one of them had Still's disease and the other one had HCV infection. The remaining one patient had no underlying disease, and showed favorable prognosis. The disease in this patient was self-limiting and the patient survived almost without any treatment. Two other patients received administration of steroids or VP-16, but nevertheless died. Our present patient also developed cerebral hemorrhage and died.

Dr. Ishii: This patient showed a very uncommon course in various senses. Professor Okada, will you please give your final comments about the present patient?

Dr. Okada (Pathology): The pathology of the liver in the present case is very interesting. We expected acute liver atrophy showing massive hepatic necrosis, but the liver at autopsy had findings suggestive of the convalescent stage of acute hepatitis. This was a surprising finding, but we must keep in mind that almost complete repair can occur in damaged livers, even in fulminant hepatitis. In the present case, we have also learned the precise mechanisms of hemophagocytic syndrome. We hope that hemophagocytic syndrome may be cured by target treatments in the near future.

Dr. Ishii: Thank you. I now conclude today's CPC. Thank you very much for your attention.