Clinical Journal of Gastroenterology (2019) 12:112–119
https://doi.org/10.1007/s12328-018-0904-y

CASE REPORT

An intensive medical care network led to successful living-donor liver transplantation in late-onset hepatic failure with disseminated *Staphylococcus aureus* infection

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Received: 4 July 2018 / Accepted: 5 September 2018 / Published online: 14 September 2018

Abstract

Here, we describe a 42-year-old male patient with late-onset hepatic failure (LOHF) due to acute-onset autoimmune hepatitis. At first, his response to steroid therapy was good, but hepatitis relapsed during steroid pulse therapy. Deterioration of liver function caused LOHF, and LOHF has a poor prognosis, particularly when it is complicated by infection. Systemic infection by *Staphylococcus aureus* resulted in a skin rash and septic pulmonary embolism, and is an absolute contraindication for liver transplantation (LT). In this treatment network, hepatologists and a transplant surgeon cooperated to overcome severe infection and their efforts led to successful transplantation. On-line hemodiafiltration is an indispensable treatment option for acute liver failure. Infection control is crucial for LT and an intensive medical care network led to successful living-donor LT.

Keywords Liver transplantation · *Staphylococcus aureus* · Skin rash · Septic pulmonary embolism

Introduction

Acute liver failure (ALF) is a fatal clinical disorder that involves sudden and severe liver injury. Abrupt loss of metabolic and immunological function in the liver leads to coagulopathy, encephalopathy, and risk for an intractable infection [1]. According to the annual nationwide survey for ALF and late-onset hepatic failure (LOHF), patients with LOHF not only have the worst prognosis but also the highest incidence of infection [2].

The most reliable treatment for ALF is liver transplantation (LT) [3]. In Japan, due to delays in the introduction of LT and a severe shortage of organ donors [4], intensive medical care plays an important role in the management of patients with ALF. In this paper, we describe a patient who was diagnosed with LOHF due to autoimmune hepatitis (AIH) at the first hospital. Furthermore, his condition was complicated by sepsis during corticosteroid (CS) therapy. While his wife declared her intention of being an organ donor, the patient was in a state of contraindication for LT due to severe systemic infection. An intensive medical treatment including antimicrobial therapy and artificial liver support (ALS) was conducted at the second hospital. Intensive medical care kept the patient in a favorable condition for 4 weeks and further blood culture test results were negative; as such, the patient was transferred to an organ transplant center. Antibiotic therapy in combination with anticoagulant therapy after removal of the catheter was effective; therefore, the patient underwent successful living-donor LT (LDLT) with his wife as the organ donor.

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We established the Tokyo–Kanagawa ALF study group 25 years ago. It was established for analyzing the mechanism and treatment of ALF by the social network system (Fig. 1). The local medical network worked very well in this case. In the beginning, intensive medical care including ALS was the only core treatment for ALF. Today, the role of intensive medical care has changed. It not only focuses on treating ALF patients, but also builds a bridge for patients to undergo LT, particularly in difficult-to-transplant patients, as reported here.

Case

A 42-year-old male patient was admitted to a local hospital because of general malaise and liver dysfunction accompanying a skin rash. His liver function was normal according to a regular medical check-up at his company 10 months ago. He had no drinking and medication history. His first symptom was general malaise and dark urine (day 0) and hepatic dysfunction was revealed during a regular medical check-up at his company 20 days after the appearance of the first symptoms (Fig. 2). On day 27, the patient visited a local hospital and underwent a blood examination. The results of the blood examination are shown in Table 1. The laboratory data indicated that total bilirubin (T-BIL) was 13.4 mg/dL, aspartate aminotransferase (AST) was 430 U/L, alanine aminotransferase (ALT) was 268 U/L, and the prothrombin time (PT%) was 44.0% of normal. Due to liver dysfunction with severe jaundice, the patient was immediately hospitalized at the local hospital. After admission, the cause of liver dysfunction was carefully scrutinized by laboratory tests, which showed an IgG of 3219 mg/dL and the presence of antinuclear antibodies at a ratio of 1:40. The patient had no history of liver dysfunction or hepatitis. To confirm a diagnosis of AIH, a liver biopsy was done via the transjugular route considering the risk of bleeding on day 40. The results of the liver biopsy showed centrilobular necrosis with intense lymphoplasmacytic infiltration and parenchymal collapses (Fig. 3a–c). The levels of serum copper (68 μg/dL) and ceruloplasmin (18 mg/dL) were low, but the rate of urinary copper excretion (69.2 μg/day) was not increased. HLA typing showed A (26, 33), B (61, 46), C (w1, w8), DR (9, 12), DQB1 (7, 9). AIH score obtained 16 points by international AIH group [5]. Therefore, the patient was diagnosed with acute onset of AIH based on blood and histological examinations. After the diagnosis, oral administration of 60 mg prednisolone was initiated on day 42. The skin rash was diagnosed as folliculitis and was observed under treatment with a topical ointment (Fig. 4a). His serum level of transaminase slowly declined to around 50 U/L, but his PT% did not improve. Therefore, steroid pulse therapy with methylprednisolone 1000 mg was started on day 55. However, his transaminase level had re-elevated by day 59. The patient developed hepatic encephalopathy grade II and was therefore transferred to a second hospital for intensive medical care including ALS therapy.

The patient had a fever of 38.2 °C and his general condition apparently deteriorated on the day he was transferred to the second hospital, which was an intensive medical care center that specialized in ALS. The patient's consciousness rapidly deteriorated, resulting in confusion. It became very difficult to do extracorporeal circulation, so the patient was intubated and placed on artificial respiratory control with continuous sedation. ALS therapy consisting of plasma exchange (PE) and on-line hemodiafiltration (HDF) under artificial ventilation was started. The details of ALS were as follows. PE was performed using a conventional separation

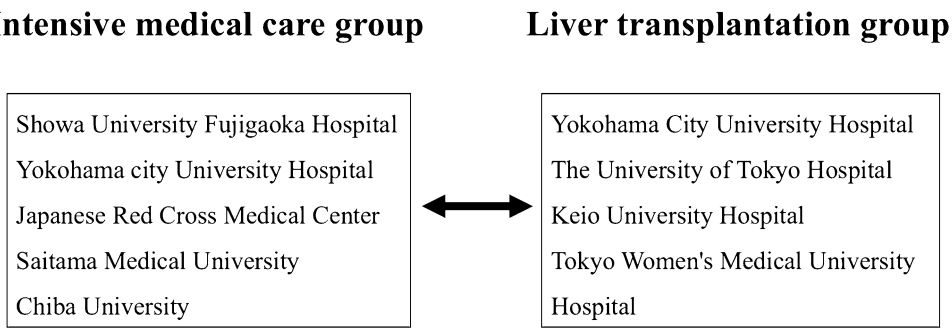

Fig. 1 The current status of Tokyo–Kanagawa ALF study group. The Tokyo–Kanagawa acute liver failure study group was founded by Dr. Yoshiba in 1995. Core members at the time of the founding were Showa University Fujigaoka Hospital, Teikyo University Mizonokuchi Hopsital, Yokohama City University Fukuura Hospital, St. Marianna University Hospital, Toho University Hospital, and Self-Defense Forces Central Hospital. The mission of this study group is the improvement of intensive medical care including standardization of artificial liver support. The majority of the members at the time of foundation have retired, and the role of liver transplantation in acute liver failure treatment has been growing year by year. Therefore, we reorganized the study group and added cooperation between intensive care and transplant medicine to our mission. Currently, the member facilities are spreading from Tokyo–Kanagawa to neighboring prefectures. This figure shows the current organization of the study group. *ALF* acute liver failure

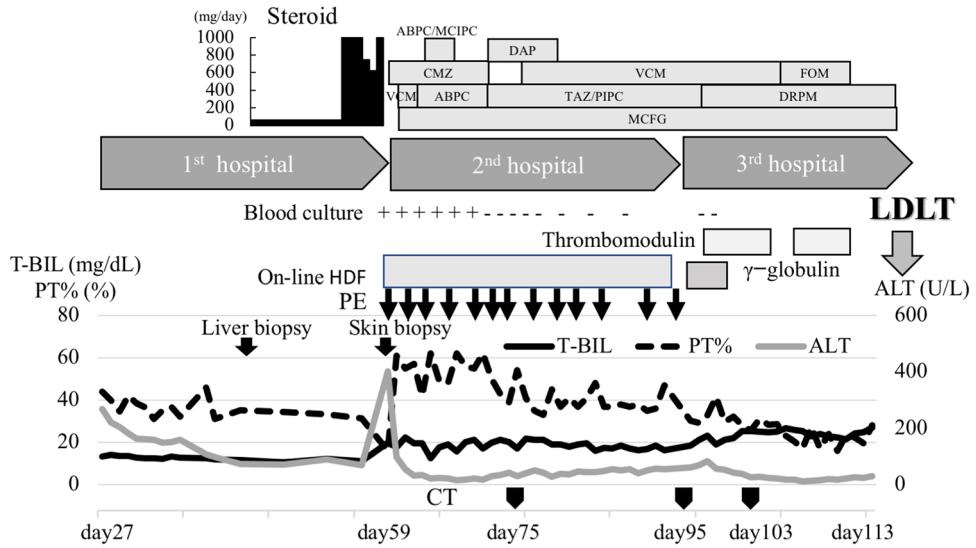

Fig. 2 Clinical course of the patient. Steroid therapy and PE were performed for AIH-induced ALF. Several combinations of antibiotics and DIC therapy including thrombomodulin and γ-globulin were used to treat the systemic infection before LDLT. *AIH* autoimmune hepatitis, *ALF* acute liver failure, *DIC* disseminated intravascular coagulation, *PSL* prednisolone, *CMZ* cefmetazole, *VCM* vancomycin, *MCFG* micafungin, *ABPC/MCIPC* ampicillin/oxacillin, *DAP* daptomycin, *TAZ/PIPC* tazobactam/piperacillin, *FOM* fosfomycin, *DRPM* doripenem, *T-BIL* total bilirubin, *PT* prothrombin time, *ALT* alanine aminotransferase, *PE* plasma exchange, *HDF* hemodiafiltration, *LDLT* living-donor liver transplantation, *CT* computed tomography, *(+)* positive, *(−)* negative

membrane (Plasmaflow OP, Asahi Kasei Medical, Tokyo) to remove the bulk of the patient's plasma and replace it with fresh human plasma. In the section of on-line HDF, concentrated dialysate (Carboster-L, Yoshindo, Toyama) was diluted with ultrapure water supplied by central system and we use it as dialysate and substitution fluid.

The HDF apparatus included DSG-3 (Nikkiso Tokyo, Japan) equipped with two endotoxin retrieval filters to dialysate at a rate of 700 mL/min. The substitution fluid was 250 mL/min taken from the dialysate. The remaining 450 mL/min dialysate was used for dialysis. The substitution fluid was delivered in pre-dilution mode. The hemodiafilter was ABH-18PA (Asahi KASEI Medical, Tokyo, Japan) made of polysulfone with a surface area of 1.8 m^2 and an ultrafiltration coefficient of 90 mL/mmHg/h (h). The operation time of the on-line HDF was 6–10 h, depending on the condition of the patient.

Given the possibility of systemic infection, two sets of blood culture samples were taken from two different locations on admission to the second hospital. Empirical antibiotic administration was started on day 60 because patients with liver failure are at high risk of infection. He was not complicated with human immunodeficiency virus infection and diabetes. An oral examination revealed multiple dental caries with root infection accompanied by gingival swelling. Oral care was started by dental hygienists and nurses. We also suspected that the skin rash was a manifestation of systemic infection (Fig. 4a). A skin biopsy was obtained from a maculopapular rash at admission. The results of the skin biopsy showed abscess formation and the presence of neutrophils around the hair follicle in the dermis (Fig. 4b). This was consistent with bacterial dissemination by blood flow.

On the morning of day 61, all four of the pre-antibiotic treatment blood culture samples were positive for Gram-positive cocci. Despite the initiation of antibiotics, the patient continued to have a high fever; therefore, vancomycin (VCM) and micafungin (MCFG) treatment was started in addition to cefmetazole (CMZ). As the Gram-positive bacteria were methicillin-susceptible *Staphylococcus aureus* (MSSA) on day 63, the antibiotic was changed from VCM to ampicillin/oxacillin (ABPC/MCIPC). After admission at the second hospital, repeated transthoracic echocardiography did not reveal vegetation or any valve complications. On day 64, septic pulmonary emboli (SPE) were found in the lung field via computed tomography (CT). Although it was very difficult to treat the MSSA systemic infection, the patient gradually regained consciousness. On day 64, the patient was able to obey our simple commands.

Drug-susceptibility testing showed that the cultured MSSA was susceptible to ABPC/MCIPC and CMZ; however, the blood culture results were persistently positive for MSSA. On day 68, an oral surgeon extracted dental caries with infected roots, and excised and drained gingiva.

It was suspected that ABPC was insufficient for controlling the systemic infection; therefore, the antibiotic was changed to tazobactam/piperacillin (TAZ/PIPC) and daptomycin (DAP) on day 71. CMZ was changed to VCM on day 76 because the blood concentration of VCM can be

Table 1 Laboratory data on admission to the first hospital

Hematology		
WBC	8000	/μL
Neutrophils	65.0	%
Lymphocytes	26.0	%
Monocytes	5.0	%
Eosinophils	4.0	%
RBC	3.89	$\times 10^6$/μL
Hb	12.8	g/dL
Ht	37.1	%
PLT	13.1	$\times 10^4$/μL
Biochemistry		
TP	5.0	g/dL
ALB	2.6	g/dL
T-BIL	13.46	mg/dL
D-BIL	10.65	mg/dL
D/T ratio	0.76	
AST	430	U/L
ALT	268	U/L
ALP	621	U/L
γ-GTP	147	U/L
LDH	322	U/L
ChE	114	U/L
BUN	9.1	mg/dL
Cr	0.79	mg/dL
Na	138.2	mEq/L
K	3.54	mEq/L
Cl	105.7	mEq/L
CRP	0.06	mg/dL
BS	82	mg/dL
HbA1c (NGSP)	5.0	%
Coagulation		
PT-INR	1.49	
PT	44.0	%
Serology		
IgG	3219	mg/dL
IgA	583	mg/dL
IgM	315	mg/dL
TSH	0.128	μIU/mL
FT3	1.47	pg/mL
FT4	1.05	ng/dL
AFP	17.8	ng/mL
DCP	20.99	mAU/mL
ANA (homogeneous pattern)	×40	
AMA	< 20 (−)	
AMA-M2	< 1.5 (−)	
Virus markers		
IgM-HA Ab	< 0.04 (−)	
HBs Ag	0.00 (−)	
HBs Ab	0.00 (−)	
HBc Ab	< 1.00 (−)	
HBV-DNA	(−)	
HCV Ab	0.09 (−)	
HCV-RNA	(−)	
IgA-HEV Ab	(−)	
EBV-IgM	< 10	
EBV-IgG	×80	
EBV-EBNA	×40	
CMV-IgM	< 0.80 (−)	
CMV-IgG	69.1	
MELD score	21	

WBC white blood cell, *RBC* red blood cell, *Hb* hemoglobin, *Ht* hematocrit, *PLT* platelet, *TP* total protein, *ALB* albumin, *T-BIL* total bilirubin, *D-BIL* direct bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γ-GTP* gamma-glutamyltransferase, *LDH* lactate dehydrogenase, *ChE* cholinesterase, *BUN* blood urea nitrogen, *Cr* creatinine, *Na* sodium, *K* potassium, *Cl* chloride, *CRP* C-reactive protein, *BS* blood sugar, *PT-INR* international normalized ratio of prothrombin time, *PT* prothrombin time, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *IgM* immunoglobulin M, *TSH* thyroid stimulating hormone, *FT3* free triiodothyronine, *FT4* free thyroxine, *AFP* α-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *ANA* antinuclear antibody, *AMA* antimitochondrial antibody, *IgM-HA Ab* anti-hepatitis A IgM antibody, *HBs Ag* hepatitis B surface antigen, *HBs Ab* hepatitis B surface antibody, *HBc Ab* anti-hepatitis B core antibody, *HCV Ab* hepatitis C virus antibody, *IgA-HEV Ab* anti-hepatitis E IgA antibody, *EBV-IgM* Epstein–Barr virus viral capsid antigen immunoglobulin M antibody, *EBV-IgG* Epstein–Barr virus viral capsid immunoglobulin G antibody, *EBV-EBNA* Epstein–Barr virus nuclear antigen, *CMV* cytomegalovirus, *MELD* model for end-stage liver disease

monitored, which is useful for estimating the pharmacokinetics of VCM. Subsequent blood cultures were negative. SPE and the skin rash slowly shrank under antibiotic treatment (Fig. 5a); however, they did not disappear during hospitalization at the second hospital. The patient maintained clear consciousness under ALS therapy. A CT scan revealed significant liver atrophy (Fig. 6a) and the patient was judged to still require LT. Both the recipient and the donor agreed to LDLT and been transferred to the third hospital on day 95.

At the third hospital, the transplant surgeons and gastroenterologists who were in charge of the patient decided to perform LT the day after the transfer after CT scans revealed liver atrophy (Fig. 6b). However, the organ transplant committee judged that the treatment for infection was insufficient because SPE and the skin rash persisted (Fig. 5b). In addition, the white blood cell (WBC) count was still elevated at 11,690/μL. Furthermore, ultrasonography revealed a thrombus in the right femoral vein. To treat the infection, the antibiotic treatment was changed from TAZ/PIPC to doripenem (DRPM), and treatment for liver failure and disseminated intravascular coagulation (DIC) continued. The catheter was changed whenever the patient had a fever, and this occurred several times. Lastly, the antibiotic treatment was changed from VCM to fosfomycin (FOM), in addition to MCFG and

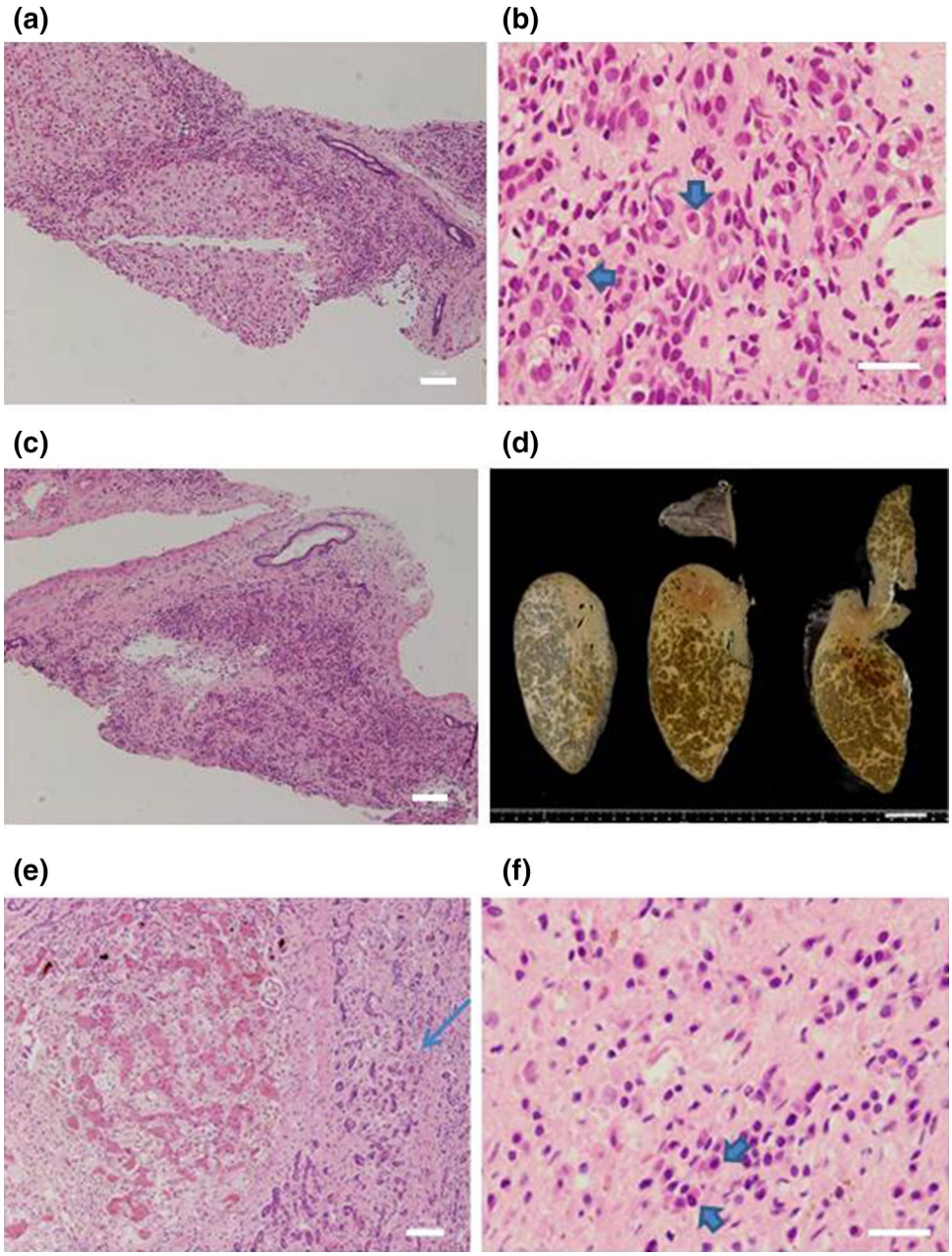

Fig. 3 Representative liver biopsy specimens and explanted liver. **a**–**c** Liver biopsy specimens. **d** Macroscopic findings from the explanted liver. **e, f** Microscopic findings from the explanted liver. (⇒: plasma cell, →: peudo-ductural formation, scale bar: 100 μm). During the first hospitalization, the liver biopsy specimen showed interface hepatitis **a** with plasma cell infiltration (**b**) and centrilobular necrosis (**c**). Macroscopically, the explanted liver was 1080 g in weight and extremely atrophic (**d**). Microscopically, massive necrosis with pseudoductural formations (**e**) and plasma cell infiltration (**f**) was observed

DRPM, based on the results of blood culture testing. After 8 weeks of antibiotic treatment, the WBC count was normal, SPE diminished (Fig. 5c) and the skin rash lesions showed crusting (Fig. 4c). Hepatic encephalopathy appeared on day 112 and the patient still required LT. After maintaining negative blood culture results for 6 weeks, the patient underwent LDLT on day 113. The explanted liver was 1080 g in weight and was extremely atrophic (Fig. 3d). The liver showed massive necrosis with pseudo-ductural formations and plasma cell infiltration (Fig. 3e, f). The postoperative course went fairly well with improvement of liver function without any infection. The patient was discharged from the third hospital on day 176.

Discussion

A 42-year-old man with acute-onset AIH developed LOHF that was complicated by sepsis. A specialist network and intensive care for sepsis and SPE led to successful LDLT. AIH usually involves the formation of chronic hepatitis [6]. It is rare for acute-onset AIH to develop into ALF. In this case, we diagnosed acute-onset AIH based on laboratory data in combination with liver biopsy results.

In our network, treatment for underlying disease usually starts as early as possible by predicting the risk of developing encephalopathy [7]. CS therapy is the established treatment for AIH; however, approximately 20% of

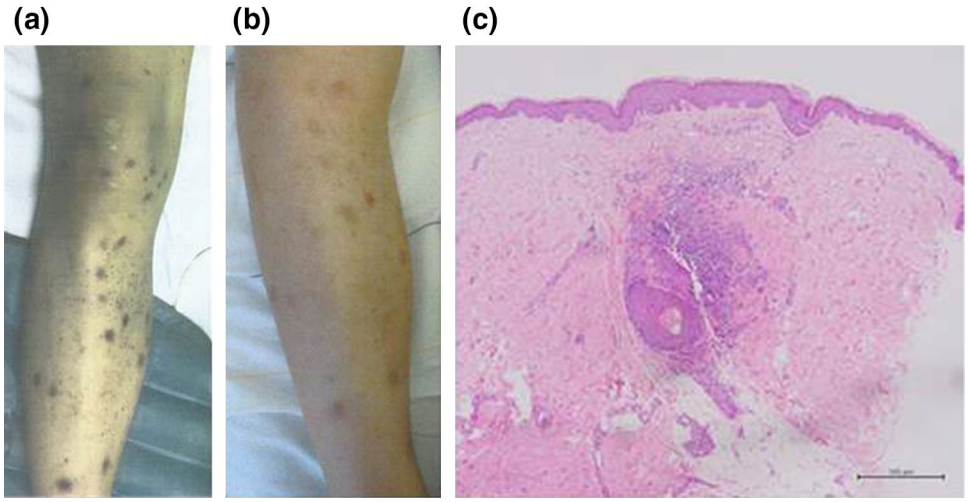

Fig. 4 Skin lesion characteristics. **a, c** Dermatological findings from the left leg. **b** Pathological findings on skin biopsy. During the second hospitalization, dermatological findings from the left leg included the presence of a systemic skin rash (**a**) that improved and showed scabbing during the third hospitalization (**c**). Pathological findings from the skin biopsy included subcutaneous abscess formation (**b**)

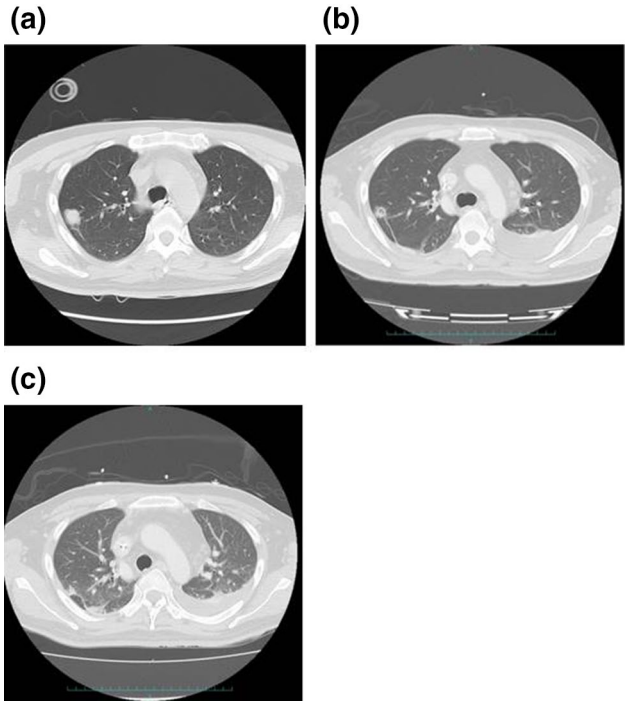

Fig. 5 Chest plain computed tomography (CT) scan findings. Plain CT scan findings on **a** day 75 at the second hospital, **b** on admission at the third hospital (day 95), and **c** on day 103. On day 64, a plain chest CT showed multiple septic pulmonary emboli (SPE). On day 75, multiple cavitation nodules with signs of feeding vessels were observed bilaterally with pleural effusion (**a**). After antibiotic treatment, multiple lung masses decreased in size on admission to the third hospital, but still remained (**b**). Cavity nodules were improved by day 103 (**c**)

patients do not respond to CSs [8]. In severe forms of AIH, patients with poor response to CSs are at risk of infection and liver failure. Methods for evaluating the risk of infection include using the model for end-stage liver disease (MELD) score before starting CS therapy [9, 10]. According to these papers, it was predicted that this case would not respond to corticosteroid therapy. LT should be done without delay in countries where LT is considered the first-line treatment. However, in Japan, other than LDLT [4], the number of LTs is very limited; as such, we had to start CS therapy even after taking into consideration the increased risk of infection.

We believe the bacterial entry site was the oral cavity or skin. Generally, we check for and treat oral caries before LT; however, because this patient's condition was so severe, we could not treat him completely, and oral care was continued after LT. A recent paper reported that MSSA was frequently isolated from the oral cavity [11]. The oral cavity should be considered a source of MSSA that can be disseminated to other body sites. In this case, severe bacterial infection was superimposed with severe hepatitis that aggravated liver function [12, 13], resulting in the development of LOHF. From the viewpoint of biological defense, 80% of macrophages in the body are present in the liver and the liver is the first line of immunological defense in the body [14]. Accordingly, patients with ALF tend to be susceptible to infection and difficult to treat. In a recent Japanese report, patients with LOHF were frequently complicated by infection and had poor prognosis [2].

In our case, we observed septemia [15] and typical findings of SPE, including multiple peripheral nodules with cavitation. Sepsis can be diagnosed when the same bacteria identified by skin biopsy are also detected in blood culture tests. Strictly speaking, bacteria should be detected in both skin and blood; however, we only detected the bacteria in the blood tests. In addition, SPE is a rare disease that occurs when thrombi-containing pathogens mixed with fibrin from an infected site undergo embolization and enter the venous circulation. Thrombi become implanted in the vascular system of the lungs and obstruct the peripheral lung artery, leading to secondary infection [16].

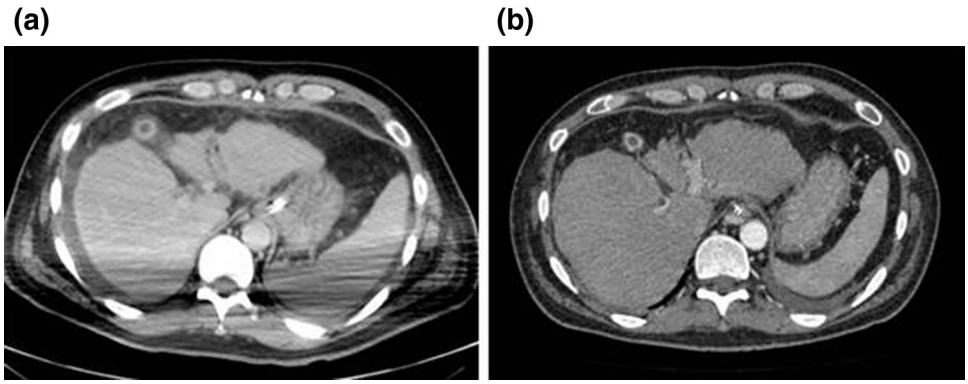

Fig. 6 Abdominal enhanced liver computed tomography (CT) scan findings. Abdominal enhanced liver CT scan findings on admission to the **a** second hospital and **b** third hospital. On admission to the second hospital, CT scan findings showed significant liver atrophy after steroid pulse therapy (**a**). On admission to the third hospital, liver atrophy was still apparent after steroid treatment and plasma exchange (PE) (**b**)

After transfer to the second hospital, they focused on treatment of the infectious disease instead of the underlying disease under ALS. Immunosuppressive therapy is not compatible with treatment for severe infection. Successful LDLT was our final treatment goal. On-line HDF can indiscriminately remove certain substances from the blood that make it difficult to maintain the antibiotic level within the target therapeutic range. The antibiotics that play a main role in MSSA treatment all have a β-lactam ring in the core structure and their effects theoretically depend on time above the minimum inhibitory concentration. During the first 5 days at the second hospital, the patient was in a critical state and the duration of ALS therapy exceeded 12 h. HDF removes small-molecular-weight drugs such as antibiotics in the body fluid by diffusion and convection. Hypoalbuminemia also decreases drug retention in systemic circulation. In conditions such as massive ascites, increased vascular permeability due to systemic inflammation results in fluid extravasation into the interstitial space, which expands the drug distribution volume in a critical state of patient. All of this results in a decrease in the blood concentration of hydrophilic drugs such as β-lactam antibiotics. This also hindered treatment of the blood infection; however, ALS was essential to maintain the patient's consciousness. Therefore, it took 9 days for the blood culture results to be negative for MSSA.

Following the guidelines for infective endocarditis and intravascular catheter-related infection [17, 18], antibiotic administration was continued after removal of the catheter at the third hospital. Catheter infections increase the risk for SPE [19] and infection with Gram-positive bacteria, such as *S. aureus* and *Staphylococcus epidermides*, can lead to SPE [20, 21]. SPE has a poor prognosis [22], with a mortality rate of 13.3%. Antibiotics should be taken for at least 4–8 weeks [20, 23]. We continued antibiotic treatment 6 weeks after the blood culture results were negative for MSSA. By continuing antimicrobial therapy after removal of the catheter for blood purification, both skin lesions and pulmonary lesions were remarkably alleviated. The patient was afebrile, the inflammatory marker levels decreased, and the infection was controlled. While the duration of antibiotic treatment before LT is unclear, in our case, cautious control of infection led to successful LDLT with the patient's wife as the donor. Furthermore, severe infection was not observed after LDLT.

In summary, a local network including a specialist for ALS and a transplant surgeon is crucial. Patients with ALF complicated by severe infection are at great risk for multiorgan failure. In such patients, ALS increases the clearance of hydrophilic drugs such as β-lactam antibiotics and several critical factors increase drug distribution volume. The establishment of adequate antimicrobial therapy in ALF is pivotal for increasing the chance of recovery and successful LT.

Compliance with ethical standards

Conflict of interest Professor Katsutoshi Tokushige received research fundings from Sumitomo Dainippon Pharma Co., Ltd. Astellas Phama Inc. Eisai Co., Ltd. TAIHO Pharmaceutical Co., Ltd. Chugai Pharmaceutical Co., Ltd. Daiichi Sankyo Pharmaceutical Co., Ltd. AbbVie GK, Takeda Pharmaceutical Company Limited. Asahi Kasei Corporation. AJINOMOTO CO., Inc. Otsuka Pharmaceutical Co., Ltd. Other authors have no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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