MATHEWS

Case Report

Mathews Journal of Case Reports

Cytokine-Induced Liver Regeneration for the Treatment of Alcoholic Liver Cirrhosis

Takuji Shirasawa[1,2,*], Luis Carlos Aguilar Cobos[3]

[1]*Ochanomizu Health and Longevity Clinic, Tokyo 101-0062, Japan*

[2]*Shirasawa Anti-Aging Medical Institute, Tokyo 101-0062, Japan*

[3]*Livant Neurorecovery Center, Guadalajara, Mexico*

ABSTRACT

Alcoholic liver cirrhosis is a chronic, progressive liver disease characterized by the formation of scar tissue, ultimately resulting in liver failure. This condition is prevalent, affecting millions of individuals worldwide. In this case report, we present a case study of a 63-year-old male patient diagnosed with decompensated alcoholic liver cirrhosis, accompanied by significant complications such as massive ascites, massive pleural effusion, hyperammonemia, renal failure, cardiopulmonary failure, and repeated hepatic coma. The cytokine-induced liver regeneration process was achieved by means of a cytokine cocktail composed of porcine hepatocyte growth factor (HGF) and FGF21. HGF and FGF21 has been shown to stimulate hepatocyte regeneration in murine models of fatty liver disease. Following a period of nine months during which the patient received cytokine treatment, there were indications of hepatic recovery. Concurrently, there was resolution of cardiopulmonary failure, cognitive dysfunction, renal failure, and hypercoagulability. This constitutes a novel strategy for the treatment of decompensated alcoholic liver cirrhosis, an incurable liver disease. To the best of our knowledge, this is the first case report providing evidence that cytokine-induced liver regeneration can ameliorate the symptoms of decompensated alcoholic liver cirrhosis. To definitively ascertain the efficacy of cytokine therapy in promoting liver regeneration as a treatment for cirrhosis, further case studies and a controlled clinical trial are imperative.

Keywords: Liver Regeneration, HGF, FGF21, Alcoholic Liver Cirrhosis, Hepatic Coma, Hepatic Failure.

INTRODUCTION

Alcoholic liver cirrhosis is a serious disease affecting millions of people worldwide. This condition is the result of prolonged alcohol consumption, which causes irreversible hepatic injury. Alcoholic liver disease (ALD) is a multifaceted condition that affects millions of individuals worldwide. The clinical entity in question is characterized by a multifaceted interplay among pathogenic processes, including alcohol metabolism, oxidative stress, inflammation, and liver injury [1].

Vol No: 11, Issue: 02

Received Date: April 30, 2026

Published Date: May 22, 2026

***Corresponding Author**

Takuji Shirasawa,

Ochanomizu Health and Longevity Clinic, Tokyo 101-0062, Japan & Shirasawa Anti-Aging Medical Institute, Tokyo 101-0062, Japan,

E-mail: takujishirasawa@icloud.com

Citation: Shirasawa T, et al. (2026). Cytokine-Induced Liver Regeneration for the Treatment of Alcoholic Liver Cirrhosis. Mathews J Case Rep. 11(2):223.

The liver is responsible for the primary metabolism of ethanol, which results in the production of acetaldehyde. This process is catalyzed by alcohol dehydrogenase, an enzyme that has been shown to be hepatotoxic and contributes to the development of fibrosis. Alcoholic consumption has been shown to result in the development of steatosis, which can subsequently lead to the onset of alcoholic hepatitis. This condition is marked by hepatic inflammation, which can ultimately result in the development of cirrhosis, a condition distinguished by hepatic scarring [2]. The precise mechanisms underlying the progression of liver damage remain to be elucidated. However, both genetic and environmental factors have been identified as contributing elements [3].

The etiology of alcoholic liver cirrhosis is multifactorial and involves alcohol consumption as a primary risk factor, in addition to other contributing factors such as genetic predispositions, gender, and the presence of coexisting liver diseases, including hepatitis [1,4]. The consequences of cirrhosis are severe, with complications including portal hypertension, ascites, and an increased risk of hepatocellular carcinoma [2,5].

With regard to the molecular pathophysiology of liver cirrhosis, hepatocyte growth factor (HGF)/c-met and fibroblast growth factor 21 (FGF21) have been reported to play a pivotal role in the progression of liver cirrhosis [6-8]. The study of knockout mice for c-Met in mice revealed that there was impaired liver regeneration after anti-FAS-induced hepatocyte apoptosis [6]. The gene therapy of hepatocyte growth factor (HGF) in a rat liver cirrhosis model has indicated that the HGF/c-Met signaling pathway exerts a suppressive effect on transforming growth factor-beta (TGF-β) signaling, which is a pivotal mediator of fibrosis in the progression of liver cirrhosis. [7]. In the context of FGF21, the study demonstrated that KO mice exhibited an exacerbation of alcohol-induced hepatic steatosis and liver injury following FGF21 depletion [8]. Conversely, the administration of rhFGF21 in WT mice resulted in a reduction of alcohol-induced hepatic steatosis and inflammation [8]. These findings suggest that FGF21 signaling holds promise as a novel therapeutic approach for the treatment of alcoholic steatohepatitis [8].

The management of alcoholic liver cirrhosis is predicated on addressing both the underlying liver disease and the underlying alcohol dependence. The predominant evidence-based practices for alcoholic liver disease include a combination of abstinence from alcohol, adequate nutritional support, and the administration of medications [9]. Specifically, patients with severe alcoholic hepatitis may be treated with corticosteroids. Patients with end-stage liver disease are considered candidates for liver transplantation [10]. The efficacy of gene therapy and molecular targeted therapy has yet to be determined.

METHOD

The cytokine and exosome cocktail formulation used in this study was designed and developed by Luis Carlos Aguilar Cobos at the Livant Neurorecovery Center, Mexico, as described previously [11-15]. In this case study, five cytokine and exosome formulations were utilized. Cytokines were extracted from porcine tissues and subsequently purified by high-performance liquid chromatography (HPLC). As indicated by Meta di Reg, the following cytokines and growth factors play a role in facilitating liver regeneration process: FGF21, adiponectin, irisin, IGF1, IGF2, HGF, IL-10, and glucagon-like peptide 1 (GLP-1). Epatrof (RGAU) EM RNs contain HGF, GCSF, SCF, IGF-1, BDNF, and FGF-2, which facilitate the neurogenesis of glutamatergic and GABAergic neurons. Antisen is a cytokine cocktail composed of MUSS EM, Neurogen AD EM, Epatrof (RGAU) AD EM, Miotrof RN JR, Coragen JR o AD, ARTIC DIV JR o AD, SAL EXO MIC, and Renagen Spleen. This combination has been shown to protect against cellular senescence. Coragen Cardi Lung contains cytokines that are extracted from porcine heart and lungs. This cytokine facilitates the development and functional rehabilitation of the heart and lungs. Renagen Spleen is a product derived from porcine splenocytes. It has been shown that this product can promote the rejuvenation of the immune system and facilitate the clearance of senescent cells. A cytokine cocktail was administered sublingually 3 times per day. The dosage of cytokines and exosome in this case study is delineated in the Result section.

The purification of cytokines was achieved through the application of a high-performance liquid chromatography (HPLC) method, employing porcine tissues as the source material. Porcine HGF and FGF21 were enriched by HPLC fractionation and ultrafiltration. Research has demonstrated that Epatrof (RGAU) EM RNs and Meta Di Reg contain the enriched fraction of porcine HGF and FGF21, respectively. Subsequently, the concentrations of these cytokines were adjusted to x1, x3, or x6 for each personalized formulation. An examination was conducted to ascertain the safety of cytokines and exosome in rodents. This investigation was reviewed by the Livant Review Committee (Livant Neurorecovery Center, Mexico).

Ethical approval of studies and informed consent.

Written informed consent was obtained from the patients. Ethical approval was reviewed by Shirasawa Anti-Aging Medical Institute Ethical Committee.

The abstinence from alcohol was meticulously monitored by the Food Diary during the follow-up process at the Ochanomizu Health & Longevity Clinic.

CASE DESCRIPTION

On November 11, 2024, a 63-year-old male patient was referred to the Ochanomizu Health & Longevity Clinic from Dokkyo University Hospital. The patient's primary complaint was recurrent hepatic coma because of decompensated alcoholic liver cirrhosis. The patient had a protracted history of alcohol consumption from an early age.

The patient's medical history revealed two notable conditions: first, the diagnosis of hemolytic uremia syndrome in 2019, and second, the subsequent development of alcoholic liver cirrhosis in the same year. In 2020, the patient exhibited signs of an acute hemorrhagic peptic ulcer, and in 2021, a diagnosis of Mallory–Weiss syndrome was made. In 2022, the patient exhibited signs of drug-induced hyperkalemia and subsequently experienced recurrent hepatic coma in 2024.

A comprehensive neurological evaluation revealed that the patient's consciousness remained intact, cognitive abilities were unimpaired, and there was an absence of hepatic coma or neurological abnormalities. A magnetic resonance imaging (MRI) scan revealed no atrophy of the cerebral cortex and no evidence of hemorrhagic or ischemic pathologies (see Figure 1A). The Memory Performance Index (MPI) score, a brief evaluation of short-term memory, was 54.93 on November 11, 2024, which is indicative of normal memory function when the MPI score exceeds 50.2 (Figure 1B). A cerebral electroencephalogram (EEG) revealed slow activity in the frontal, central, parietal, and occipital leads (see Figure 1C). These findings align with the concept of hyperammonemia resulting from liver cirrhosis. P300 electroencephalogram (EEG) responses at the left frontal (F3, black line) and central frontal (Fz, blue line) regions recorded after high-pitched sounds on November 11, 2024, revealed dissociated responses with three peaks of 5~8 μV2 (Figure 1E). The findings of this study also revealed abnormalities in the cellular metabolism of the neuronal cells of the cerebral cortex.

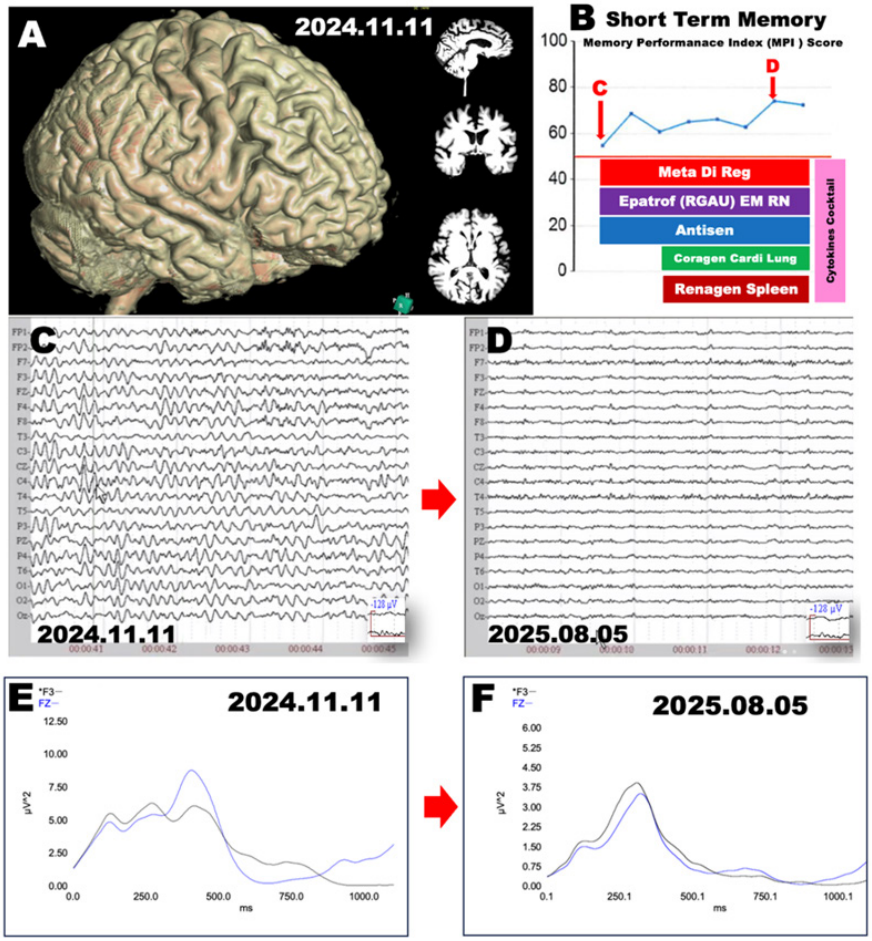

Figure 1. MRI scan, short-term memory, electroencephalogram, and P300-evoked EEG response before and after cytokine-induced hepatogenesis and neurogenesis.

A. 3D structure of the brain reconstructed in silico (using Expert INTAGER software) from MR T1-weighted images with 1-mm sagittal slices. The right panel shows conventional 2D T1-weighted images of sagittal (upper), coronal (middle), and horizontal (lower) sections.

B. The graph in the upper panel illustrates the progression of short-term memory. Short-term memory is evaluated through the utilization of the MPI (Memory Performance Index) score. The MPI score on November 11, 2024, is indicated by arrow C, and the MPI score on August 5, 2025, is indicated by arrow D. The lower panel illustrates the cytokines utilized in this case.

C, D. Electroencephalographs (EEGs) recorded on November 11, 2024 (C) and August 5, 2025, (D) are shown.

E, F. P300 electroencephalogram (EEG) responses at the left frontal (F3, black line) and central frontal (Fz, blue line) regions recorded after high-pinched sounds on November 11, 2024, are shown in Figure E. P300 EEG responses at the left frontal (F3, black line) and central frontal (Fz, blue line) regions recorded after high-pinched sounds on August 5, 2025, are shown in Figure F.

The patient's blood chemistry results indicated significant findings for hepatic function. Hypoalbuminemia (Alb 2.7 g/dL), elevated serum ammonia levels (Ammonia 151 μg/dL), and decreased ChE (68 U/L) were observed. Other hepatic function tests were within normal limits. The AST, ALT, and LDH levels were recorded at 20 U/L, 10 U/L, and 200 U/L, respectively. The findings indicated the presence of hepatic failure that could be characterized as moderate to severe (see Figure 2). The results of the blood chemistry panel also revealed elevated levels of creatinine (1.55 mg/dL), BNP (42.9 pg/mL), D-dimer (14.58 μg/mL FEU), and CA125 (298 U/mL). The results indicated that hepatic failure is accompanied by mild renal failure, mild heart failure, and hypercoagulopathy (Figure 2).

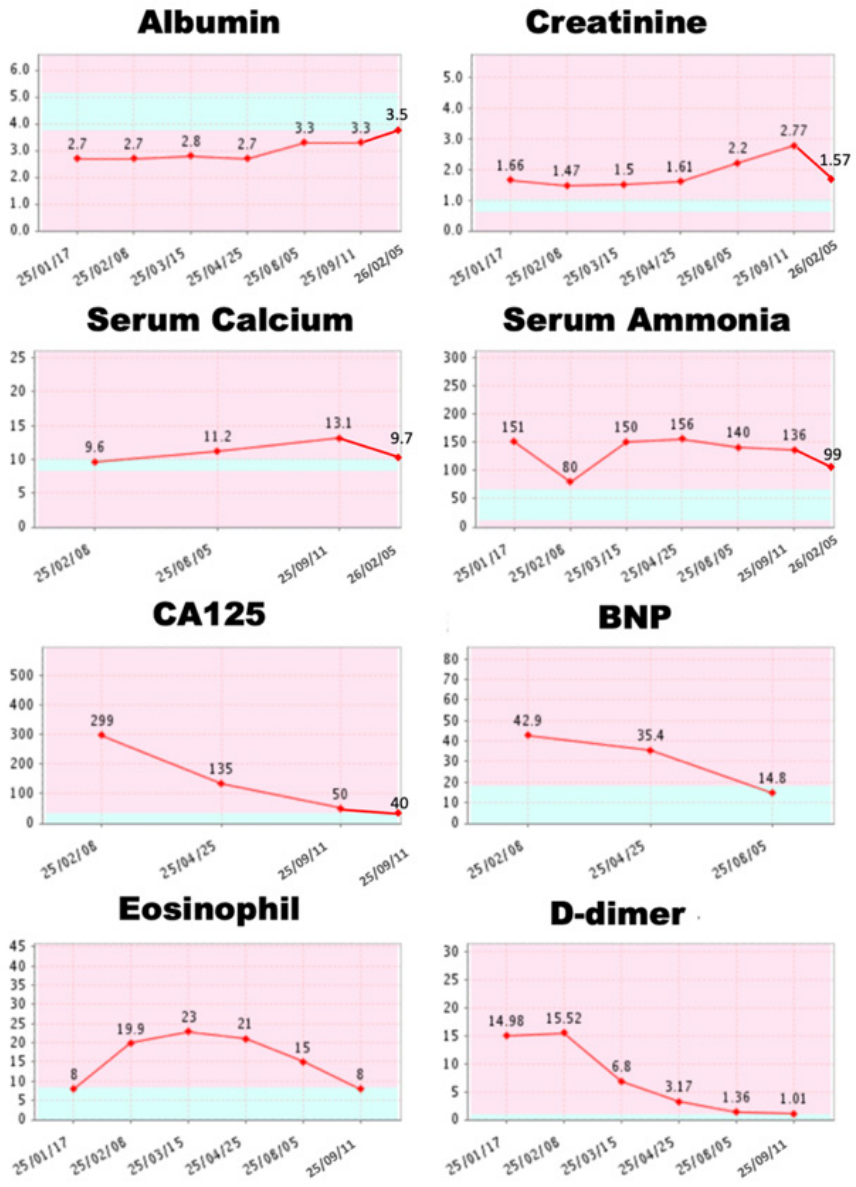

Figure 2. Clinical Course of Biomarkers.

The values of the serum albumin concentration (g/dL), creatinine concentration (mg/dL), serum calcium concentration (mg/dL), serum ammonia concentration (μg/dL), CA125 concentration (U/mL), BNP concentration (pg/mL), eosinophil percentage, and D-dimer concentration (μg/mL FEU) during cytokine treatment from January 17, 2025, to February 5, 2026, are graphically presented.

A CT scan of the abdomen performed on January 17, 2025, revealed atrophy of the liver and the presence of substantial ascites (see asterisk, Figures 3A and 3C). A virtual laparoscopic view of the liver was created in silico from a 3D MR image. These observations revealed that the liver surface exhibited an irregular topography, a finding consistent with the pathophysiology of alcoholic liver cirrhosis (Figure 3E).

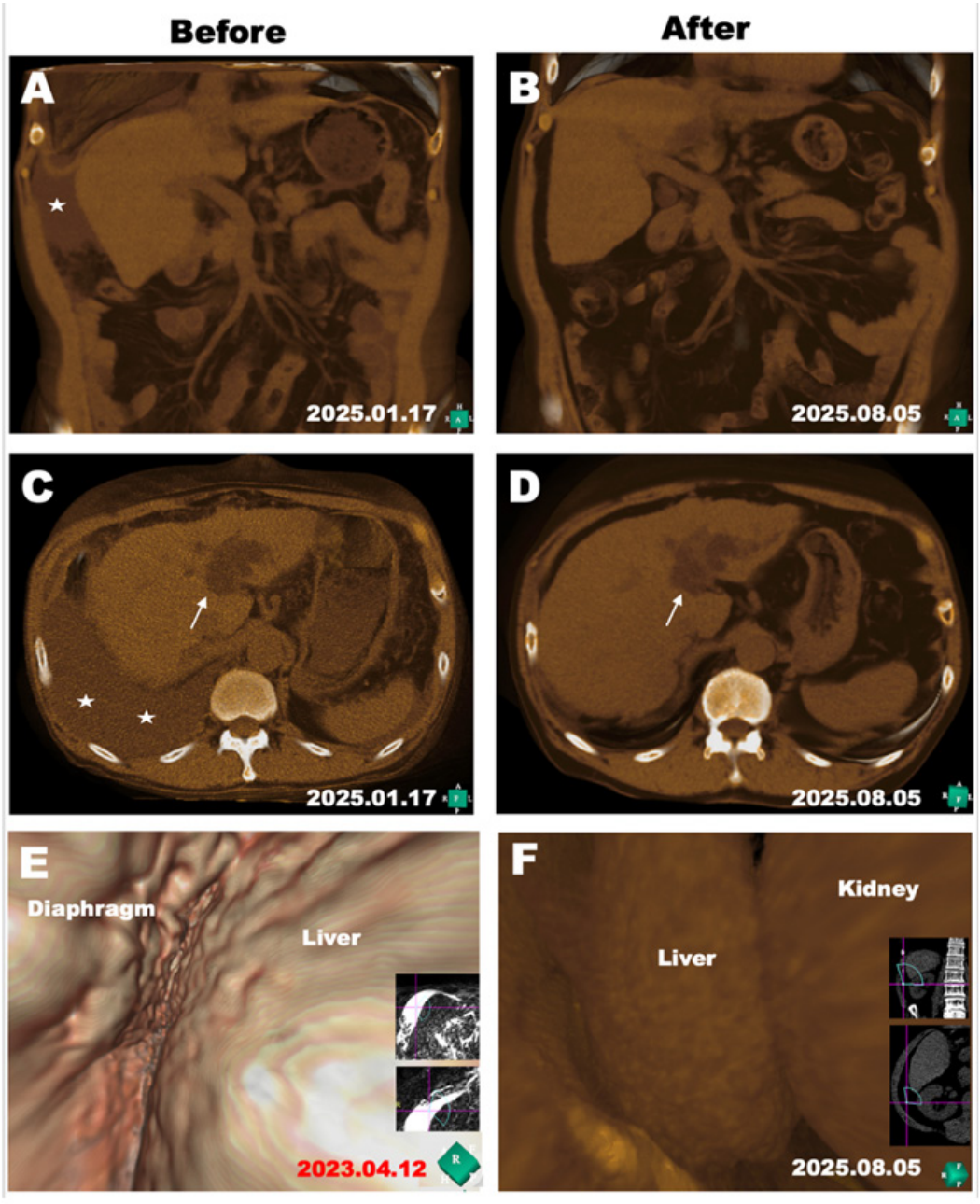

Figure 3. Morphological evaluation of the liver before and after cytokine-induced liver regeneration. MRI scan on April 12, 2023 (E), CT scans on January 17, 2025 (A, C), and on August 05, 2025 (right panel), before and after cytokine cocktail treatment.

A., B. 3D structure of the liver (frontal view) reconstructed in silico using Expert INTAGER software from 1-mm CT slices before and after cytokine cocktail treatment. Asterisk indicates ascites.

C., D. 3D structure of the liver (coronal view) before and after cytokine cocktail treatment. Asterisks indicate ascites. An arrow indicates a low-density area of liver cirrhosis pathology.

E., F. Laparoscopic in silico images of the diaphragm, liver, and kidney before and after cytokine cocktail treatment.

E. Virtual endoscopic view of the liver and diaphragm reconstructed from MRI slices recorded on April 12, 2023.

F. The virtual endoscopic view of the liver and kidney was reconstructed from a series of CT slices recorded on August 5, 2025. The position, angle, and window of the camera view are indicated by insects on the right side.

A CT scan of the lungs revealed substantial pleural effusion in the right thorax, accompanied by atelectasis of the right lower lobe (see Figures 4A and 4E). A virtual bronchoscopy view of the right lower bronchus revealed no obstructive changes. These findings indicate that atelectasis of the lower lobe of the right lung may be a consequence of substantial pleural effusion. As shown in Figure 4C, the pulmonary function test revealed obstructive changes, with a percentage FEV1.0 of 70.6%. This functional abnormality is compatible with the massive pleural effusion that limits the expansion of the right lung.

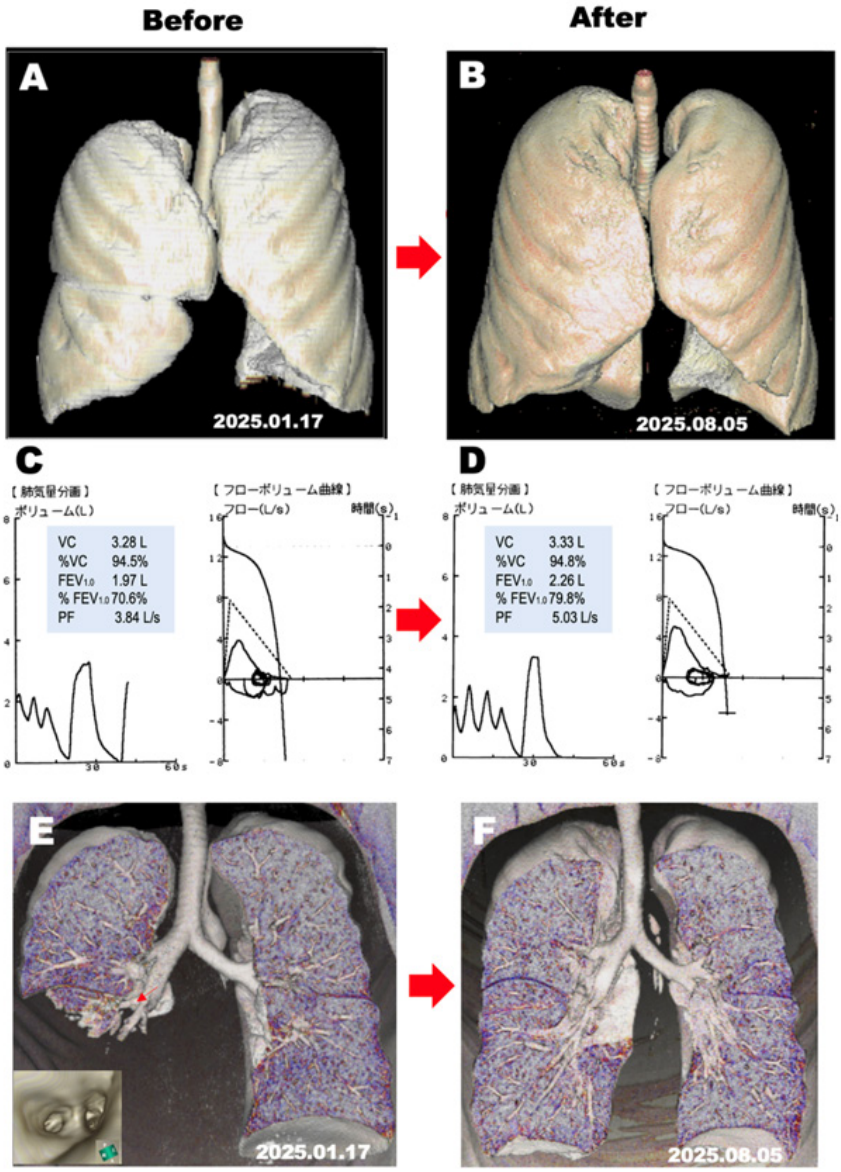

Figure 4. A morphological and physiological evaluation of the lung was conducted before and after cytokine-induced liver regeneration. A CT scan and pulmonary function tests were performed on January 17, 2023 (left panel), and August 5, 2025 (right panel), prior to and following the administration of a cytokine cocktail.

A. B. 3D structure of the lung (frontal view) reconstructed in silico using Expert INTAGER software from 1-mm CT slices before and after cytokine cocktail treatment.

C, D. Pulmonary function tests recorded on January 17, 2023 (left panel), and August 5, 2025 (right panel), were performed prior to and following the administration of a cytokine cocktail.

Figure E, F: Three-dimensional representation of the bronchus and lung before and after treatment with a cytokine cocktail.

E. A frontal cutting view of the bronchus and lung was reconstructed from a series of CT slices recorded on January 17, 2023 (see left panel). This dataset was collected prior to the administration of a cytokine cocktail. The insect displays a virtual bronchoscopy view of the right lower lobe bronchus.

F. Frontal cutting view of the bronchus and lung reconstructed from a series of CT slices recorded on August 5, 2025 (right panel), after the administration of a cytokine cocktail.

On March 15, 2025, an echocardiogram was performed to assess cardiac function (see Figure 5A). Although the ejection fraction (EF) of the left ventricle was within normal limits (EF 62.7%), resistance was observed during the diastolic phase as the left ventricle expanded (see Figure 5A, indicated by the red arrow). The results of the study indicated that the patient's heart failure was not attributable to a cardiac origin. Rather, the findings suggested that the patient's heart failure was a consequence of massive pleural effusion in the right thorax (see Figures 5B and 5C). On January 17, 2025, diagnostic thoracentesis was performed. Analysis of the pleural fluid revealed the presence of noninflammatory exudate, with no malignant cells identified. These findings indicate that the pleural effusion was attributable to liver cirrhosis, as opposed to inflammation or malignancy within the right thorax.

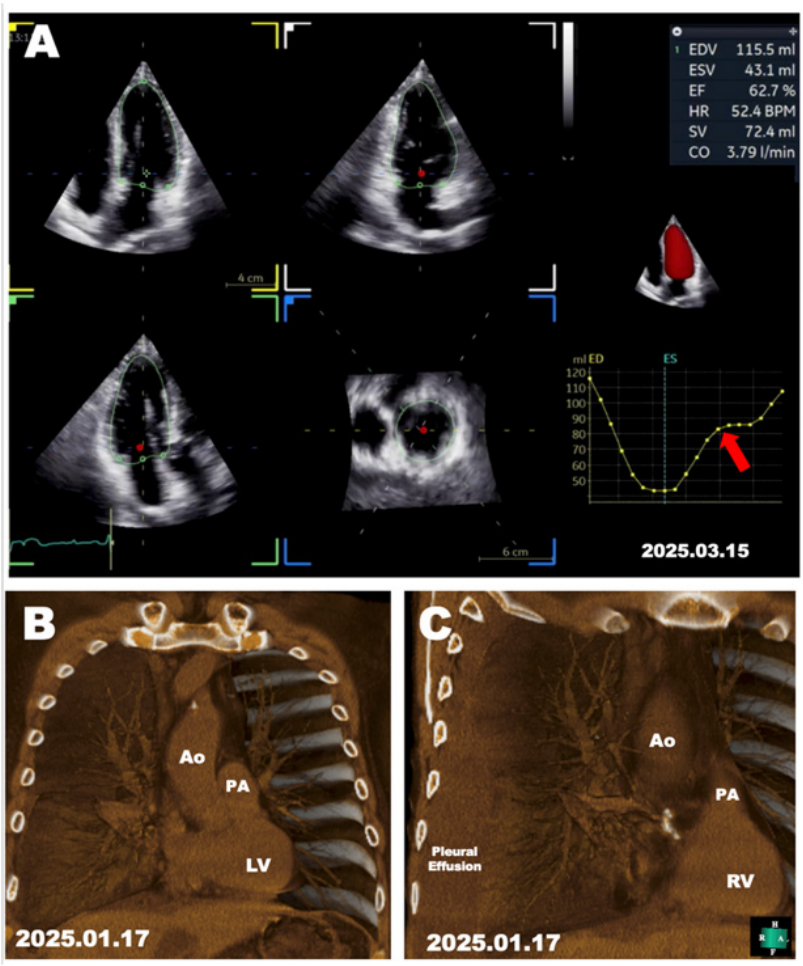

Figure 5. An echocardiogram of the heart in axial view showed left ventricular function. The following acronyms are displayed in the upper right corner: EDV (end-diastolic volume), ESV (end-systolic volume), EF (ejection fraction), HR (heart rate), SV (stroke volume), and CO (cardiac output). The dynamics of the left ventricle are illustrated on the right lower side of the image.

B: The patient's frontal cutting view of both pulmonary arteries and pulmonary veins, as well as the left ventricle (LV), pulmonary artery (PA), and aorta (Ao), was recorded on January 17 prior to the administration of the cytokine cocktail.

C: The right lateral cutting view of the right pulmonary artery, pulmonary vein, right ventricle (RV), pulmonary artery (PA), aorta (Ao), and pleural effusion in the right pleura was recorded on January 17 prior to the administration of the cytokine cocktail.

The clinical data indicated that the patient's condition met the diagnostic criteria for decompensated alcoholic liver cirrhosis, accompanied by hepatic coma, massive ascites, massive pleural effusion, mild renal failure, mild heart failure, and mild respiratory failure. The patient was referred to the transplantation surgery section of the University of Tokyo Hospital. However, despite meticulous efforts, the surgeon was unable to locate a suitable donor.

The process of liver regeneration was induced through the application of a cytokine cocktail comprising HGF and FGF21 (see Figure 1B). Previous research has shown that HGF and FGF21 promotes hepatocyte regeneration in a murine model of fatty liver disease [7,8].

The patient was administered a cytokine cocktail containing the following medications: The following pharmaceuticals were administered from November 11, 2024, to August 5, 2025: The pharmaceutical regimen consisted of Meta Di Reg (concentration x6), 4.0 ml, administered three times per day; Epatrof (RGAU) EM RN (concentration x3), 4.0 ml, administered three times per day; and Antisen (concentration x6), 3.0 ml, administered three times per day. On February 8, 2025, the cytokine cocktail was supplemented with 4.0 ml of Renagen Spleen (concentration x3), which was administered three times per day, and 4.0 ml of Coragen Cardi Lung (concentration x1), which was administered three times per day.

As indicated by this research, Meta Di Reg and Epatrof (RGAU) EM RNs contain HGF and FGF21. Antisen contains a combination of cytokines that facilitate neurogenesis. Coragen Cardi Lung contains cytokines and exosomes, which are known to facilitate the regeneration of the heart and lungs. The composition of the Renagen Spleen includes cytokines such as IL-10, which function to regulate inflammatory responses (Figure 1B).

On August 5, 2025, an electroencephalogram (EEG) revealed a substantial decrease in slow-wave activity across all leads, indicating a complete recovery from hepatic coma (see Figure 1D). Furthermore, the P300 electroencephalogram (EEG) responses at the left frontal (F3, black line) and central frontal (Fz, blue line) regions recorded after high-pinched sounds exhibited synchronized responses, with one major peak of 3.75 μV^2 (see Figure 1F).

On February 5, 2026, a comprehensive blood chemistry panel revealed a significant increase in serum ammonia concentration to 3.5 g/dL and a concurrent decrease in serum ammonia concentration to 151 μg/dL and serum ChE to 159 U/L. Concurrently, the patient's other hepatic function tests exhibited normalcy. The AST, ALT, and LDH levels were recorded at 21 U/L, 9 U/L, and 220 U/L, respectively. These findings suggest that the administration of a cytokine cocktail induced hepatogenesis, leading to the production of albumin and the subsequent detoxification of ammonia (Figure 2). The decrease in the level of CA125, a biomarker associated with cancer, further corroborates the hypothesis that the catabolism of proteins in hepatocytes is substantially increased (see Figure 2).

Renal function exhibited a transient decline during cytokine therapy; however, both creatinine levels and serum calcium levels stabilized by December 5, 2026 (see Figure 2). An elevated D-dimer level substantially improved following cytokine treatment. These findings indicated a notable improvement in hypercoagulability associated with liver cirrhosis on September 11, 2025 (see Figure 2).

The patient exhibited a transient allergic reaction, characterized by eosinophilia, during cytokine treatment. The precise nature of the patient's allergy, whether it pertains to cytokines or to exosomes, remains uncertain. To date, no other case of eosinophilia has been documented for cytokine treatment in our clinic. In any case, the cytokine known as Renagen Spleen, which contains IL-10, was administered from February 8, 2025, with the objective of suppressing allergic reactions. The findings of the study indicate a possible resolution of eosinophilia with the Renagen Spleen (Figure 2).

A CT scan performed on August 5, 2025, revealed the clearance of ascites, as indicated by the absence of fluid accumulation in the abdominal cavity (see Figure 3B, D). However, the presence of low-density regions was still observed in the hilar region of the liver (see Figure 3D, indicated by the arrow). A virtual laparoscopic view of the surface of the liver revealed a marked improvement in surface irregularity (Figure 3F).

Coragen Cardi Lung was administered to enhance cardiopulmonary function. This cytokine mixture comprises cytokines and exosome extracts derived from the lungs and heart. The therapeutic intervention was initiated on February 8, 2025, with the objective of enhancing cardiopulmonary function. As demonstrated in Figure 2, the elevated level of BNP tended to decrease following the administration of Coragen Cardi Lung. A CT scan of the lung revealed the clearance of substantial pleural effusion (see Figure 4B, F) concomitant with an enhancement in pulmonary function, as evidenced by an increase in the FEV1.0 (see Figure 4D). A significant decrease in BNP levels was observed on August 5, 2025, suggesting a concomitant improvement in cardiopulmonary function. The results of the study suggest that Coragen Cardi Lung may contribute to the resolution of cardiopulmonary failure.

As of April 24, 2026, the patient continues to receive treatment with cytokines to ensure the maintenance of hepatic function. The patient's daily life significantly changed following the initiation of cytokine treatment. He derives great pleasure from engaging in leisure activities such as golfing and skiing, which he partakes in as a healthy senior individual.

DISCUSSION

In the present case report, we report for the first time that cytokine-induced liver regeneration can ameliorate the symptoms of decompensated alcoholic liver cirrhosis with massive ascites, massive pleural effusion, hyperammonemia, renal failure, cardiopulmonary failure, and repeated hepatic coma. The cytokine cocktail has been shown to contain HGF and FGF21, factors that have been shown to promote hepatocyte regeneration [6-8]. A substantial body of clinical data presented in this case report has indicated a strong correlation between the regeneration of hepatocytes in the liver and a marked improvement in symptoms. This constitutes a novel strategy for the treatment of decompensated alcoholic liver cirrhosis, an incurable liver disease.

The purification of cytokines from organic porcine tissues was accomplished by means of high-performance liquid chromatography (HPLC) fractionation, a method that is described in the Method section (Livant Neurorecovery Center, Mexico). In the course of the fractionation process, an assessment was conducted for the quality and quantity of cytokines contained in each purification process. These cytokines have undergone a safety evaluation in rodents prior to clinical use. Subsequent to this, clinical application of these cytokines by sublingual administration to a total of more than 300 patients over the course of the past six years has been undertaken, with no adverse reactions observed at the Ochanomizu Health & Longevity Clinic from 2018 to 2026 [11-15].

As illustrated in Figure 6, the pathogenesis of alcoholic liver cirrhosis is initiated by chronic ethanol exposure. As indicated by the literature, this exposure results in oxidative metabolism within hepatocytes via the alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1) pathways [16]. This metabolic activity yields acetaldehyde, a potent cytotoxin, and generates reactive oxygen species (ROS). These factors give rise to three primary pathogenic axes: (1) Oxidative stress: It has been shown that reactive oxygen species (ROS) can induce lipid peroxidation, which can consequently compromise membrane integrity [17]. Second, Kupffer cell activation is observed. Proinflammatory signaling, initiated by TNF-alpha and interleukins, is responsible for orchestrating a chronic inflammatory response [18]. Third, stellate cell activation is observed. In response to injury, quiescent stellate cells undergo a transformation into myofibroblasts, which leads to excessive collagen deposition in the space of Disse [19]. The progression of liver diseases is driven by a series of mechanisms that collectively contribute to the development of a pathological continuum. This continuum begins with a healthy state and progresses sequentially to steatosis (fatty infiltration), fibrosis, and ultimately, a nodular, cirrhotic liver characterized by irreversible architectural distortion [20,21].

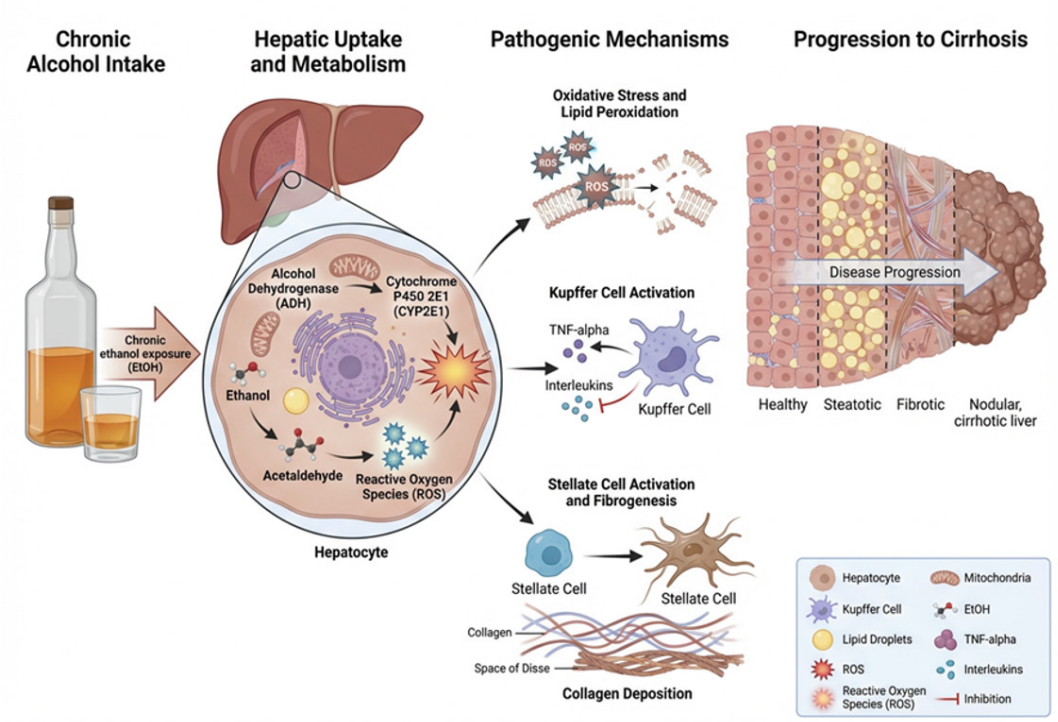

Figure 6. Illustrates the pathological progression of alcoholic liver cirrhosis.

As illustrated in Figure 7, FGF21 functions as a critical metabolic hormone that is predominantly synthesized in the liver. It plays dual roles as both a stress-responsive biomarker and a therapeutic effector in chronic liver disease [22,23]. Under physiological conditions, hepatocytes maintain baseline secretion of FGF21 into the bloodstream. However, during the progression from healthy tissue to liver cirrhosis, several pathological triggers—specifically oxidative stress (ROS), proinflammatory cytokines, and lipotoxicity—induce compensatory upregulation of FGF21 expression [24]. This increase in hepatic FGF21 is positively correlated with the clinical severity of cirrhosis [24]. FGF21 functions as a protective metabolic agent to counteract liver injury. This includes the downregulation of lipotoxicity and the mediation of anti-inflammatory effects [25].

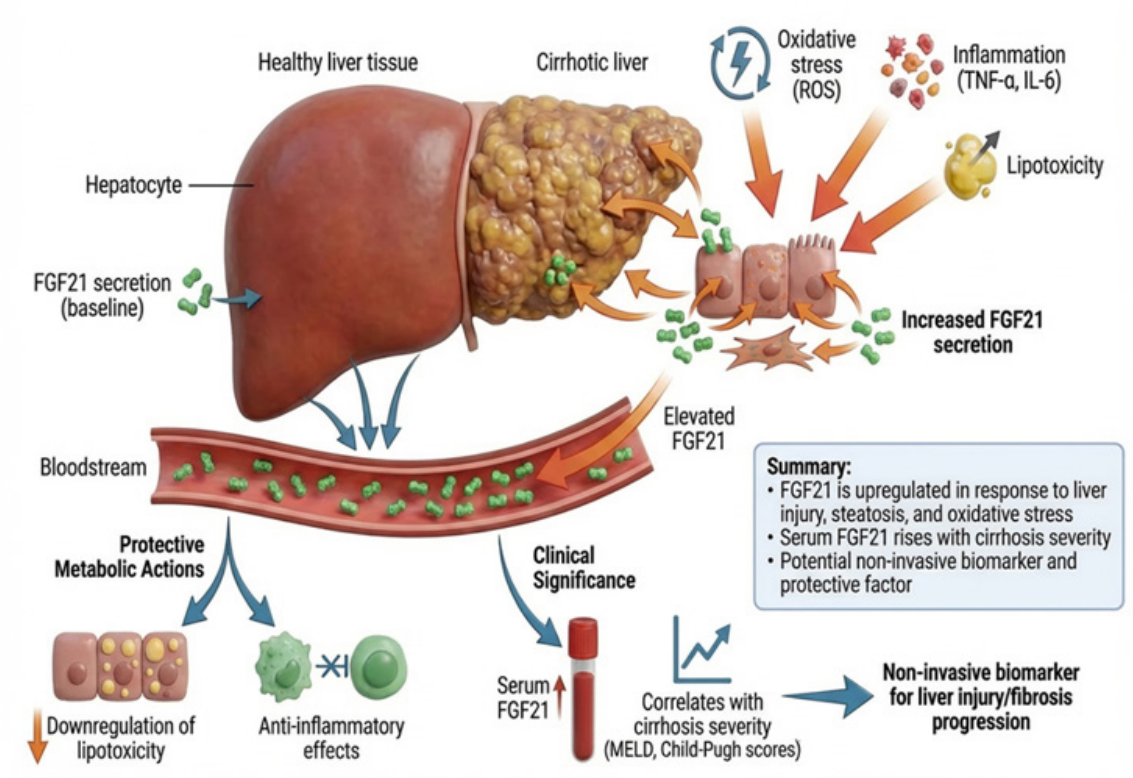

Figure 7. Illustrates the pathological role of FGF21 in the progression of alcoholic liver cirrhosis.

As shown in Figure 8, FGF21 plays a pivotal role in orchestrating hepatic recovery following injury. In response to hepatic insult, hepatocytes undergo a process of damage or destruction. In turn, these hepatocytes release FGF21, which is known to act in an autocrine or paracrine fashion [26]. FGF21 exerts its effects by binding to a transmembrane receptor complex consisting of FGF Receptor 1 (FGFR1) and the essential co-receptor Klotho [27]. The formation of this ligand–receptor complex initiates a robust intracellular signaling cascade, which is characterized by the phosphorylation and activation of three primary pathways. The following genes were identified: STAT3, ERK1/2 (MAPK), and PI3K/AKT [28]. The activated mediators in question have been observed to translocate to the nucleus, thereby upregulating regeneration gene expression [29]. This process has been found to be specifically targeted toward the production of cyclins [30]. This molecular shift facilitates cell cycle progression, driving the transition of quiescent hepatocytes into mitosis (hepatocyte division). This synchronized proliferation ultimately replaces damaged tissue, thereby restoring structural integrity and functional capacity to the regenerated liver [29].

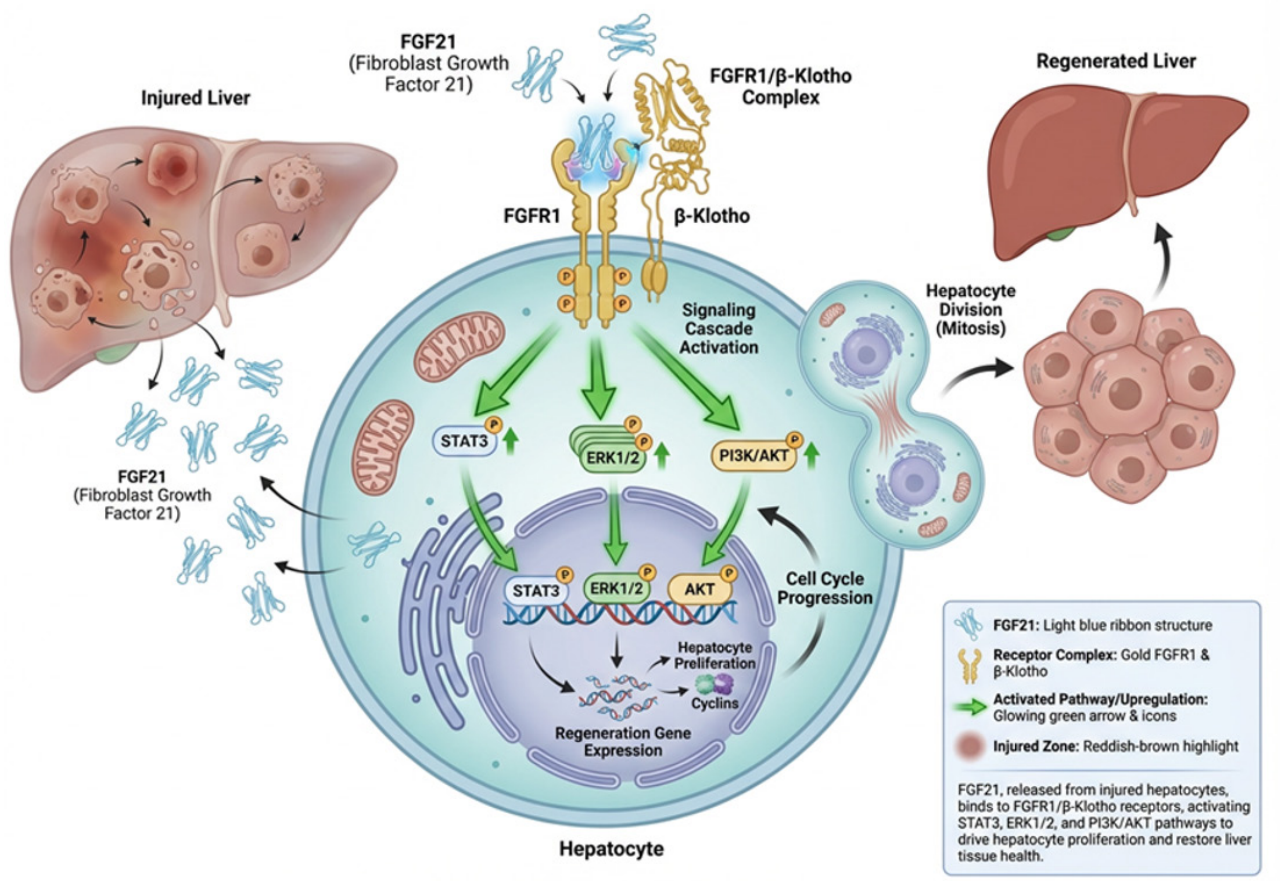

Figure 8. Illustrates the molecular biology of FGF21 in the process of liver regeneration.

In addition to the administration of Meta Di Reg, which contains FGF21, Epatrof (RGAU) was also administered to facilitate the hepatogenesis and neurogenesis of the patient. Research has demonstrated the presence of hepatocyte growth factor (HGF) in Epatrof (RGAU) and Meta Di Reg, suggesting a potential mechanism for facilitating hepatocyte proliferation and liver regeneration. This process is thought to occur through the HGF/c-MET axis [31]. The HGF/c-MT signal has been demonstrated to suppress fibrosis of liver tissue [7]. This suppression is achieved by inhibiting TGF-ß signaling and downregulating hepatic stellate cell activation [7].

In the process of hepatic repair, HGFs play a pivotal role in cell proliferation, as evidenced by the activation of the PI3K/AKT and MAPK pathways [6,32]. Conversely, evidence has demonstrated that metabolic stress or nutritional stress activates FGF21 via FGFR1/ß-KL activation. Consequently, this process results in the upregulation of STAT3, ERK1/2 (MAPK), and PI3K/AKT pathways, thereby enhancing hepatic metabolism in the repair process [28,33]. The hypothesis that both ligand and receptor systems may synergistically contribute to the hepatic repair process is postulated. In a recent study, Kang et al. demonstrated that GDF-15 and FGF21 exhibit a synergistic effect in facilitating metabolic

adaptation in cases of metabolic liver disease [34]. GDF15 has been shown to regulate body and fat mass, as well as to prevent diet-induced hepatic steatosis. In contrast, FGF21 has been demonstrated to upregulate insulin sensitivity, energy expenditure, and thermogenesis [34]. It is of interest to ascertain the manner in which GDF15 functions in a synergistic manner during cytokine treatment in conjunction with HGF and FGF21.

It has been demonstrated that HGF promotes systemic regeneration through a variety of mechanisms, including the facilitation of DNA repair and genomic stability, the expression of anti-apoptotic effects, and the preservation of cellular integrity [31]. Research has demonstrated that, given the patient's alcohol consumption, alcohol can induce substantial metabolic impairment in both liver and brain cells. As previously delineated, the process of cytokine-induced neurogenesis possesses the capacity to replace damaged brain cells [12]. As indicated in this case report, analogous cellular replacements may be occurring in other systemic tissues, including the liver, lungs, heart, and kidneys.

As indicated by other contributors to clinical improvement, abstinence, nutritional recovery, and supportive medical care with vitamins B1, B2, B6, B12, and folate would synergistically work with cytokine treatment in the present case.

The primary limitation of this case study is its status as a solitary, uncontrolled case report. To definitively ascertain the efficacy of cytokine therapy in promoting liver regeneration as a treatment for cirrhosis, further case studies and a controlled clinical trial are imperative.

In summary, the present case offers compelling evidence to support the hypothesis that multi-organ extract-base cytokine and growth factor therapy, with a focus on HGF and FGF21 signaling, has the potential to establish a novel therapeutic paradigm capable of treating advanced decompensated cirrhosis and its associated systemic complications.

CONCLUSION

In this case report, we present a case study of a 63-year-old male patient diagnosed with decompensated alcoholic liver cirrhosis, accompanied by significant complications such as massive ascites, massive pleural effusion, hyperammonemia, renal failure, cardiopulmonary failure, and repeated hepatic coma. A cytokine cocktail containing porcine HGF and FGF21 was applied. Nine months after the initiation of cytokine treatment with abstinence, nutritional support, and supportive medical care, there were indications of hepatic recovery. Concurrently, there was resolution of cardiopulmonary failure, cognitive dysfunction, renal failure, and hypercoagulability. This constitutes a novel strategy for the treatment of decompensated alcoholic liver cirrhosis, an incurable liver disease. To the best of our knowledge, this is the first case report showing that cytokine-induced liver regeneration can ameliorate the symptoms of decompensated alcoholic liver cirrhosis.

ACKNOWLEDGEMENTS

The authors would like to thank Ms. Sayuri Sato and Ms. Fernanda Diaz for the preparation of this manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Dugum M, McCullough A. (2015). Diagnosis and Management of Alcoholic Liver Disease. J Clin Transl Hepatol. 3(2):109-116.
2. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. (2021). Liver cirrhosis. Lancet. 398(10308):1359-1376.
3. Morgan MY, Sharma M, Atkinson SR. (2021). Genetic and Environmental Susceptibility to Alcoholic Hepatitis. Clin Liver Dis. 25(3):517-535.
4. Tsochatzis EA, Bosch J, Burroughs AK. (2014). Liver cirrhosis. Lancet. 383(9930):1749-1761.
5. Tapper EB, Parikh ND. (2023). Diagnosis and Management of Cirrhosis and Its Complications: A Review. JAMA. 329(18):1589-1602.
6. Huh CG, Factor VM, Sánchez A, Uchida K, Conner EA, Thorgeirsson SS. (2004). Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proc Natl Acad Sci U S A. 101(13):4477-4482.
7. Ueki T, Kaneda Y, Tsutsui H, Nakanishi K, Sawa Y, Morishita R, et al. Hepatocyte growth factor gene therapy of liver cirrhosis in rats. Nat Med. 5(2):226-230.
8. Liu Y, Zhao C, Xiao J, Liu L, Zhang M, Wang C, et al. (2016). Fibroblast growth factor 21 deficiency exacerbates chronic alcohol-induced hepatic steatosis and injury. Sci Rep. 6:31026.

9. Caputo F, Domenicali M, Bernardi M. (2019). Diagnosis and Treatment of Alcohol Use Disorder in Patients With End-Stage Alcoholic Liver Disease. Hepatology. 70(1):410-417.

10. Louvet A, Thursz MR, Kim DJ, Labreuche J, Atkinson SR, Sidhu SS, et al. (2018). Corticosteroids Reduce Risk of Death Within 28 Days for Patients With Severe Alcoholic Hepatitis, Compared With Pentoxifylline or Placebo-a Meta-analysis of Individual Data From Controlled Trials. Gastroenterology. 155(2):458-468.e8.

11. Shirasawa T, Cobos LCA. (2022). Cytokine-induced Neurogenesis for Alzheimer's Disease and Frontotemporal Dementia. Personalized Medicine Universe 11(1):27-32.

12. Shirasawa T, et al. (2023). Cytokine-induced Neurogenesis Can Reverse Cognitive Decline in Alzheimer's Disease. Mathews J Case Rep. 8(3):97.

13. Shirasawa T, et al. (2023). Cytokine-Induced Neurogenesis in Charcot-Marie-Tooth neuropathy with Connexin 32 Gene Mutation. Mathews J Case Rep. 8(7):118.

14. Shirasawa T, et al. (2024). Cytokine-Induced Neurogenesis for Bipolar Disorder: A Case Study. Mathews J Case Rep. 9(4):163.

15. Shirasawa T, et al. (2024). Cytokine-induced Neurogenesis for the Prevention and Treatment of Alzheimer's Disease. Mathews J Case Rep. 9(9):187.

16. Cederbaum AI. (2012). Alcohol metabolism. Clin Liver Dis. 16(4):667-685.

17. Wu D, Cederbaum AI. (2005). Oxidative stress mediated toxicity exerted by ethanol-inducible CYP2E1. Toxicol Appl Pharmacol. 207(2 Suppl):70-76.

18. Grønbaek H, Sandahl TD, Mortensen C, Vilstrup H, Møller HJ, Møller S. (20120. Soluble CD163, a marker of Kupffer cell activation, is related to portal hypertension in patients with liver cirrhosis. Aliment Pharmacol Ther. 36(2):173-180.

19. Liu B, Zhou Z, Jin Y, Lu J, Feng D, Peng R, et al. (2022). Hepatic stellate cell activation and senescence induced by intrahepatic microbiota disturbances drive progression of liver cirrhosis toward hepatocellular carcinoma. J Immunother Cancer. 10(1):e003069.

20. Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, et al. (2018). Alcoholic liver disease. Nat Rev Dis Primers. 4(1):16.

21. Gao B, Bataller R. (2011). Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 141(5):1572-1585.

22. Liu Z, Peng Y, Li S, Lin Y, Huang Y, Chen W, et al. (2023). Increased circulating FGF21 level predicts the burden of metabolic demands and risk of vascular diseases in adults with type 2 diabetes. BMC Endocr Disord. 23(1):272.

23. Zhang Y, Liu Z, Zhou M, Liu C. (2018). Therapeutic effects of fibroblast growth factor 21 against atherosclerosis via the NF κB pathway. Mol Med Rep. 17(1):1453-1460.

24. Xu K, He BW, Yu JL, Kang HM, Zheng TT, Chen ZY, et al. (2024). Clinical significance of serum FGF21 levels in diagnosing nonalcoholic fatty liver disease early. Sci Rep. 14(1):25191.

25. Yu Y, Bai F, Liu Y, Yang Y, Yuan Q, Zou D, et al. (2015). Fibroblast growth factor (FGF21) protects mouse liver against D-galactose-induced oxidative stress and apoptosis via activating Nrf2 and PI3K/Akt pathways. Mol Cell Biochem. 403(1-2):287-299.

26. Rosoff DB, Wagner-DeTurck J, Perlstein T, Reitz J, Jung J, Blaney H, et al. (2026). Genetic evidence that FGF21 signaling reduces problematic alcohol use and alcohol-related liver disease. J Hepatol. S0168-8278(26)00077-2.

27. Kuro-O M. (2019). The Klotho proteins in health and disease. Nat Rev Nephrol. 15(1):27-44.

28. Cao Z, Xie Y, Yu L, Li Y, Wang Y. (2020). Hepatocyte growth factor (HGF) and stem cell factor (SCF) maintained the stemness of human bone marrow mesenchymal stem cells (hBMSCs) during long-term expansion by preserving mitochondrial function via the PI3K/AKT, ERK1/2, and STAT3 signaling pathways. Stem Cell Res Ther. 11(1):329.

29. Cui X, Sun Q, Wang H. (2025). Targeting fibroblast growth factor (FGF)-21: a promising strategy for metabolic dysfunction-associated steatotic liver disease treatment. Front Pharmacol. 16:1510322.

30. Ng R, Song G, Roll GR, Frandsen NM, Willenbring H. (2012). A microRNA-21 surge facilitates rapid cyclin D1 translation and cell cycle progression in mouse liver regeneration. J Clin Invest. 122(3):1097-108.

31. Nakamura T, Sakai K, Nakamura T, Matsumoto K. (2011). Hepatocyte growth factor twenty years on: Much more than a growth factor. J Gastroenterol Hepatol. 26(Suppl 1):188-202.

32. Usatyuk PV, Fu P, Mohan V, Epshtein Y, Jacobson JR, Gomez-Cambronero J, et al. (2014). Role of c-Met/phosphatidylinositol 3-kinase (PI3k)/Akt signaling in hepatocyte growth factor (HGF)-mediated lamellipodia formation, reactive oxygen species (ROS) generation, and motility of lung endothelial cells. J Biol Chem. 289(19):13476-13491.

33. Kaur N, Gare SR, Shen J, Raja R, Fonseka O, Liu W. (2022). Multi-organ FGF21-FGFR1 signaling in metabolic health and disease. Front Cardiovasc Med. 9:962561.

34. Kang SG, Choi MJ, Jung SB, Chung HK, Chang JY, Kim JT, et al. (2021). Differential roles of GDF15 and FGF21 in systemic metabolic adaptation to the mitochondrial integrated stress response. iScience. 24(3):102181.