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Stem Cell Discovery

Human umbilical cord blood-derived mononuclear cell transplantation for umbilical hernia and hepatic hydrothorax in primary biliary cirrhosis*

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ABSTRACT

Cell therapy was proposed as a potential treatment intervention for liver cirrhosis recently due to the fact that the therapeutic protocol for primary biliary cirrhosis (PBC)-associated refractory umbilical hernia and hepatic hydrothorax is not well defined currently. We report herein the case of a 58-year-old woman who received routine treatments for PBC, which developed into an incarcerated hernia and uncontrolled hydrothorax. This subject's condition was significantly improved and maintained stable condition after receiving human umbilical cord blood-derived mononuclear cell (CBMC) transplantation. Consequently, this new strategy may be a potential treatment option for the refractory umbilical hernia and hydrothorax caused by PBC. However, sufficient data from large-scale controlled and double-blinded clinical trials are needed to further confirm the treatment efficacy and long-term safety before this cell transplantation can be used as a regular therapy for liver cirrhosis.

Keywords: Primary Biliary Cirrhosis (PBC); Umbilical Hernia; Hepatic Hydrothorax; Human Umbilical Cord Blood-Derived Mononuclear Cell (CBMC) Transplantation

1. INTRODUCTION

Primary biliary cirrhosis (PBC) is an immune-mediated chronic progressive inflammatory liver disease that leads to the destruction of small interlobular bile ducts, progressive cholestasis, and, eventually, fibrosis and cirrhosis of the liver, commonly necessitating liver transplantation [1,2]. PBC primarily affects women with a prevalence of up to 1 in 1000 women over 40 years of age [2]. Ursodeoxycholic acid (UDCA) is currently the only FDA-approved standard medical treatment for PBC. Up to 2/3 patients with PBC may have a normal life expectancy with appropriate doses of UDCA administration. However, 1/3 patients do not adequately respond to UDCA therapy and consequently may need additional medical therapy and/or liver transplantation, especially those in advanced stage [2,3]. New treatment interventions need to be explored for those patients with late-stage PBC due to the limitation of liver transplantation, hindered by the organ donor shortage and complications associated with rejection and immunosuppression. Recently, cell therapy has been proposed as a potential treatment intervention for liver cirrhosis.

We report herein one case diagnosed with PBC that developed into an incarcerated hernia and uncontrolled hydrothorax after routine treatments. Human umbilical cord blood-derived mononuclear cell (CBMC) transplantation was recommended for this subject's refractory condition because she refused surgical treatment. This subject was discharged from the hospital at one week following two cell transplantations and showed that liver function and general condition have improved. A six-month follow-up showed similar improvements. This preliminary data suggested CBMC transplantation may have beneficial effects on patients with late-stage liver cirrhosis and associated umbilical hernia and hydrothorax [4,5].

2. CASE REPORT

A 58-year-old woman was admitted to the 2nd Affiliated Hospital of Kunming Medical College with a 9-month history of abdominal distention and tachypnea on

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December 23rd, 2010. Physical examination showed: poor general condition, slight scleral icterus, coarse breath sounds in left lung, absent breath sounds in right lower lung, abdominal distension and soft, umbilical protrusion on the abdominal wall, positive shifting dullness of abdomen, and edema on both lower extremities. Laboratory analysis revealed low levels of serum albumin (27 g/L; normal range is 35 - 55 g/L) and cholinesterase (1755 U/L; normal range is 3500 - 10,000 U/L), prolonged prothrombin time, positive test result of antimitochondrial antibodies (AMA)-M2. Liver biopsy observed destroyed middle and small bile ducts. No obstruction of large bile duct was found through magnetic resonance cholangiopancreatography (MRCP). X ray of chest showed a large amount of pleural effusion in the right chest and a few in the left side. B-ultrasound clued liver injury with reduced liver volume, widened portal and splenic veins, splenomegaly, and massive ascites. This subject was diagnosed with PBC based on above findings.

Therapy was initiated with orally administration of UDCA 25 mg/kg/day, spironolactone 100 mg/day and furosemide 40 mg/day. 25 g/day of human albumin was infused. Thoracentesis and drainage tube placed into the patient's right chest were operated in order to treat hydrothorax at two days after admission. A totally of 4100 ml of yellow turbid fluid was drained. The drainage tube was removed five days later when the shortness of breath was relieved. This subject's condition had been stable for the next month in the hospital with above treatments but aggravated with a large amount of pleural effusion, incarcerated umbilical hernia with part of the small intestine and ascites as contents and spontaneous bacterial peritonitis afterwards. In the following two months, surgical manual reduction to umbilical hernia, thoracentesis drainage and abdominal paracentesis were performed and antibiotics were administered to relieve the symptoms. This subject refused to receive surgical treatment.

Allogeneic CBMC transplantation was recommended as a further therapeutic option because umbilical hernia and hydrothorax were recurrent and gradually aggravated after routine treatment interventions. The treatment protocol and patient consent were approved by the local institutional review board of the 2nd Affiliated Hospital of Kunming Medical College under the auspices of the National Ministry of Health. The treatment procedure was clearly explained to this subject and her family members and the informed consent was obtained before each initiation of cell transplantations. Human umbilical cord blood (hUCB) was obtained from informed, healthy donors after normal spontaneous vaginal deliveries in according with the sterile procurement guidelines in the hospital. The procedure for CBMC preparation, including hUCB collection and mononuclear cell extraction, cultivation and harvest, was reported in a previous publication [6]. Two CBMC transplantations were performed and 5×10^7 CBMCs, containing 1.0% - 2.0% $CD34^+$ cells as determined by flow cytometry, were transfused per time. The first infusion was processed through the hepatic artery on April 6th, 2011 and another infusion through intravenous injection two weeks later. No adverse effect was observed during and after the cell transplantation.

Dramatic alleviation on abdomen pain, umbilical hernia and pleural effusion was shown following the first cell transplantation. The levels of serum albumin (33.5 g/L) and cholinesterase (5484 U/L) were significantly increased and the liver function was normal at six days after two cell transplantations. In addition, the general condition, including the complexion and appetite, was significantly improved. This subject was discharged at one week after two cell transplantations on a stable condition with no recurrence of umbilical hernia and pleural effusion. Orally administration of UDCA (250 mg, twice per day) was continued after discharge without other treatments. Six months after discharge, stable improvements were still observed on the general condition and liver function. This subject had good appetite and her weight had gained 7 kilograms. The levels of serum albumin (40 g/L) and cholinesterase (4800 U/L) remain the normal range. CT examination on November 23rd, 2011 showed a few pleural effusions in the right chest and a small amount of ascites.

3. DISCUSSION

Liver cirrhosis represents the final common pathological outcome for the majority of chronic liver diseases caused by a variety of factors, such as PBC. Umbilical hernia is a common complication in approximately 20% of patients with cirrhosis and uncontrolled ascites [7]. The umbilical hernia may develop into leakage, ulceration, rupture and incarceration that can be serious and cause around 30% of mortality rate [8]. Paracentesis applied to drainage ascites for reducing the pressure of abdominal cavity is not effective for majority patients and may lead to incarceration of the umbilical hernia due to the decreased tension. Surgery is a treatment option for incarcerated umbilical hernia but this is considered to be high risks with increased perioperative morbidity and mortality on cirrhotic patients with poor liver function [9]. Furthermore, the recurrence rate of umbilical hernia after surgical therapy is as high as 60% [10]. Therefore, there is currently no primary option to treat refractory umbilical hernias in patients with liver cirrhosis.

Hepatic hydrothorax occurs in 0.4% - 12.2% of cirrhotic patients [11]. Tube thoracostomy and mechanical pleurodesis are the standard treatment for recurrent symptomatic hydrothorax. Video-assisted thoracic surgery has

also been used to control pleural effusion [12]. However, the therapeutic effects from above treatments are limited. In this case, umbilical hernias and hydrothorax were recurrent and uncontrolled by the conventional treatments. Consequently, this subject developed hernias incarceration, whereas the therapeutic protocol for cirrhosis-associated refractory umbilical hernia and hepatic hydrothorax has not been well defined.

Stem cell-based therapy is of potential value in tissue regeneration and replacement and represents a unique opportunity for the treatment of liver cirrhosis. To date, the most common source of stem cells is bone marrow and many studies proved that the bone marrow stem cells contribute functionally and significantly to liver fibrosis not only in animal models [4,13,14] but also in patients [5,15-17]. However, bone marrow aspiration for patients with liver cirrhosis, especially at the late-stage, is an invasive procedure with high risks due to their bleeding tendency and poor general condition. Alternatively, hUCB may be a preferable source for stem cell transplantation to safely treat non-hematopoietic conditions as CBMCs are easy to obtain and have greater proliferative capacity, primitive ontogeny, lower immunogenicity and lower risk of graft versus-host disease [18-21].

CBMCs are comprised of a heterogenous population of hematopoietic and mesenchymal stem cells, endothelial progenitor cells, and immature immunological cells, capable of differentiating into multiple cell lineages [4, 22]. One research group confirmed the differentiation of CBMCs into hepatocytes in three different ways, namely co-culture with injured liver cells, growth factor-assisted culture, and CBMC transplantation in animal models of liver injury [23]. Study results showed that transplanted hUCB-derived $CD34^+$ cells fused with hepatocytes of NOG mice without liver injury, lost their hematopoietic phenotype, and began hepatocyte-specific gene transcription [24]. It has been reported that umbilical cord blood does contain mesenchymal stem cells (MSCs), which were able to differentiate into hepatocyte-like cells under appropriate induction conditions, and can serve as an alternative source of MSCs to bone marrow [25,26]. In addition, recent studies demonstrated that the transplanted hUCB-derived stem cells successfully incorporated into the liver of recipient animals and differentiated into functional hepatocyte-like cells that expressed hepatocyte-specific markers [27-30].

Furthermore, the therapeutic effects of CBMC transplantation have been studied in animal cirrhotic models. The histopathology of liver tissue in cirrhotic rats was significantly improved by intrahepatically transplanted CBMCs through replacing the damaged hepatocytes and decomposing the surrounding collagen fiber, including the decrease of hepatocellular necrosis, inflammatory infiltration and fibroplasias, and the resolution of fibrosepta [31]. It has been suggested that infused hUCB-derived MSCs differentiated to hepatocyte-like cells and significantly reduced the expression of transforming growth factor b1 (TGF-b1), collagen type I and α-smooth muscle actin (α-SMA) to inhibit the fibrogenesis/cirrhogenesis and recover liver function in CCl4-induced cirrhotic rats [32]. Intrahepatical transplantation of hUCB-derived MSCs could significantly improve the survival of rats with acute hepatic necrosis and the underlying mechanisms involved may include the transdifferentiation of MSCs into hepatocyte-like cells and targeted migration of these cells to liver lesion sites [33]. It has also been showed that hUCB-derived MSCs could improve insulin resistance in rats with CCl4-induced liver cirrhosis, thereby contributing to glucose homeostasis [34]. In addition, transplantation of microencapsulated hepatic-like cells derived from umbilical cord blood cells could preliminarily alleviate the symptoms in rat models with acute hepatic failure, which may be related to the immunosuppressive and substitution effects and liver repair promotion of the transplanted cells [35]. These *in vivo* findings provide a rationale for the therapeutic benefit of CBMC transplantation on liver cirrhosis although the underlying mechanism need to be further investigated.

Encouragingly, the treatment results in this case study showed that CBMC transplantation was well tolerated by this subject with refractory umbilical hernias and hepatic hydrothorax caused by PBC. Although this subject's condition continued to deteriorate after routine treatments, remarkable improvements were observed shortly following CBMC transplantation without the intervention of diuretic and human serum albumin. Moreover, stable improvements of this subject's general condition and liver function were still observed at six months after the treatment.

In summary, umbilical hernia and hepatic hydrothorax are common complications of liver cirrhosis and the treatment remains difficult due to the increased risks following surgical interventions. This case report indicates that CBMC transplantation may represent a promising therapeutic strategy for liver cirrhosis and associated refractory umbilical hernia and hydrothorax. However, sufficient data from large-scale controlled and double-blinded clinical trials are needed to further confirm the treatment efficacy and long-term safety.

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