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Case Report

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Regenerative Treatment of Liver Cirrhosis Using Allogeneic Adipose-Derived Mesenchymal Stem Cells: A Case Report

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Abstract

End-stage liver cirrhosis and chronic liver failure are life-threatening, irreversible conditions characterized by hepatocellular dysfunction, fibrosis and impaired regenerative capacity. Although liver transplantation is an effective therapy, it is often inaccessible due to donor scarcity, rejection risks and prohibitive costs, creating a high unmet medical need for novel therapies. Mesenchymal Stem Cell (MSC) transplantation represents a promising alternative, with Adipose Tissue-derived MSCs (AT-MSCs) serving as a potential source due to their high proliferation and ability to differentiate into hepatocyte-like cells. This case report details a 69-year-old male with chronic liver cirrhosis and portal hypertension treated with a regenerative protocol of allogeneic AT-MSCs. A total of 160 million viable cells were administered *via* intravenous infusion over four sessions (June 2024-December 2025). Clinical status and biochemical markers were monitored monthly to assess safety and efficacy. Following treatment, the patient exhibited significant clinical stabilization and normalization of liver enzymes (SGOT and SGPT). Symptoms such as fatigue and weakness markedly improved and the patient reported an overall increase in energy levels. No adverse events or infusion-related complications were observed and follow-up assessments indicated no further disease progression. Allogeneic AT-MSC therapy is a safe and effective intervention for enhancing the clinical status of patients with advanced liver cirrhosis. The precise mechanisms underlying the therapeutic effects of AT-MSCs remain inadequately understood. Nonetheless, numerous studies suggest that the hepatoprotective properties of AT-MSCs are primarily linked to a paracrine effect mediated by soluble factors, rather than the differentiation capabilities of the cells themselves. These findings suggest that AT-MSCs represent a viable alternative or bridging therapy to transplantation, directly addressing the critical gap in current treatment options.

Keywords: Liver cirrhosis; AT-MSCs; Regenerative medicine; Liver enzyme

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Introduction

Chronic liver diseases represent a considerable challenge to global health, resulting in approximately two million deaths each year worldwide, which accounts for nearly 3.5% of all annual fatalities. In Asia, Acute-on-Chronic Liver Failure (ACLF) is predominantly attributed to hepatitis B virus infection, with reported mortality rates varying from 63%-72.3% [1]. The causes of chronic liver disease encompass viral infections such as Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) alcoholic and non-alcoholic steatohepatitis, autoimmune disorders and genetic factors [2]. Ongoing hepatic inflammation and immune dysfunction facilitate fibrogenesis by activating inflammatory pathways, recruiting macrophages and monocytes and stimulating hepatic stellate cells, which results in excessive deposition of extracellular matrix and progressive liver fibrosis [3].

Liver fibrosis represents a pathological hallmark of the majority of chronic liver diseases, characterized by an abnormal accumulation and distribution of extracellular matrix components [4]. If not addressed promptly, liver fibrosis may advance to cirrhosis, leading to liver dysfunction, liver failure and hepatocellular carcinoma [5].

At present, aside from supportive care, there is no specific treatment that markedly enhances survival rates in patients suffering from advanced liver failure [6]. Supportive management encompasses the use of antibiotics for infections, corticosteroids for severe alcoholic hepatitis, lactulose and rifaximin for hepatic encephalopathy, vasopressors and albumin for hepatorenal syndrome, as well as artificial liver support systems like the Molecular Adsorbent Recirculating System (MARS). Nevertheless, these methods improve clinical parameters without significantly changing the disease prognosis or long-term survival outcomes [7].

Currently, liver transplantation is regarded as the most effective treatment for end-stage liver disease. However, its widespread use is constrained by a shortage of donor organs, high expenses, surgical complications and the necessity for lifelong immunosuppression [8]. Consequently, there is an urgent need for the development of alternative therapeutic strategies for liver cirrhosis. In this regard, regenerative medicine has surfaced as a promising therapeutic avenue, with cell-based therapies presenting new opportunities for liver regeneration. Cell transplantation is considered a less invasive and potentially more cost-effective method aimed at promoting hepatic regeneration and restoring liver structure and function [9]. While isolated hepatocytes have been utilized for cell transplantation, their limited availability, poor long-term survival *in vitro* and functional deterioration following cryopreservation limit their clinical use [10].

Mesenchymal Stem Cells (MSCs) have recently attracted significant interest as a potential source for liver regeneration [11]. MSCs can be obtained from various tissues, such as bone marrow, adipose tissue and dental pulp and they demonstrate a high capacity for proliferation and multilineage differentiation, including the ability to differentiate into hepatocyte-like cells [12]. Among the various types of stem cells investigated, including embryonic stem cells, induced pluripotent stem cells, hematopoietic stem cells and MSCs, the latter have garnered increasing attention due to their immunomodulatory characteristics, paracrine effects and a favorable safety profile [13]. Bone Marrow-derived Mesenchymal Stem Cells (BM-MSCs) are the most frequently utilized MSCs in clinical research pertaining to liver disease. Nevertheless, BM-MSCs exhibit several drawbacks, such as invasive collection methods, low cell yield, premature senescence during *in vitro* expansion and diminished therapeutic effectiveness when administered to elderly or chronically ill patients [14]. Furthermore, autologous BM-MSC therapy has shown short-term safety and enhancement in liver function, yet it has not demonstrated significant survival advantages in cases of advanced liver disease [15]. These drawbacks may be linked to the compromised functionality of autologous MSCs, the advanced age of patients and inadequate cell dosages [16].

To address these limitations, alternative sources of Mesenchymal Stem Cells (MSCs) have been investigated. Adipose Tissue-derived MSCs (AT-MSCs) and Umbilical Cord-derived MSCs (UC-MSCs) have garnered increasing attention due to their plentiful availability, ease of collection without inflicting harm on the donor and enhanced capabilities for proliferation and differentiation [17]. AT-MSCs and UC-MSCs both effectively reduce liver fibrosis; however, AT-MSCs show faster expansion and higher early yield, enabling timely therapeutic use. Notably, AT-MSCs possess low immunogenicity, which permits their application in allogeneic contexts without necessitating Human Leukocyte Antigen (HLA) matching, thus facilitating the swift provision of standardized, high-quality MSC products for clinical use [18]. Additionally, AT-MSCs have been demonstrated to differentiate into hepatocyte-like cells when stimulated with specific growth factors and chemical agents [19]. Despite evidence supporting the safety and efficacy of autologous MSC therapy, clinical data on allogeneic AT-MSCs in liver cirrhosis remain limited. Therefore, this study presents a clinical case of liver cirrhosis treated with intravenously administered allogeneic AT-MSCs, demonstrating improvements in clinical and biochemical parameters and stabilization of liver function.

Case Report

Patient data and health background

A 69-year-old male with a documented history of Chronic Liver Disease was admitted to JEEVASA Health Care USA (Institute of Longevity Research & Hospital, Mohali, Punjab, India) for assessment and continued management of Liver Cirrhosis accompanied by Portal Hypertension. His medical history is notable for a cholecystectomy conducted in 2010, followed by a diagnosis of liver cirrhosis in 2012. Other comorbidities included a nasal polyp identified in 2019, a COVID-19 infection during the period of 2020 to 2021 and an episode of typhoid fever with bronchitis in 2022. In that same year, he was diagnosed with Grade II Esophageal Varices and subsequently underwent endoscopic band ligation. Over time, the patient exhibited clinical and radiological signs indicative of portal hypertension and hypersplenism. The patient reported symptoms of increasing abdominal distension, bilateral pedal edema, general weakness, decreased appetite and disrupted sleep. At the time of presentation, there was no indication of active gastrointestinal bleeding, hepatic encephalopathy or ascites. Clinical examination revealed that the patient was alert and oriented. An abdominal examination showed distension and bilateral pedal edema was noted. No indications of acute hepatic decompensation were detected.

Baseline laboratory tests conducted on 5 October 2024 indicated stable hemoglobin levels at 15.4 g/dL and a platelet count of 2.96 lakh/mm^3. The renal function parameters were satisfactory, with serum creatinine

measured at 1.10 mg/dL and blood urea at 27.39 mg/dL. Liver function tests showed elevated transaminase levels, with Serum Glutamic Oxaloacetic Transaminase (SGOT) at 94.6 U/L and Serum Glutamic Pyruvic Transaminase (SGPT) at 32.9 U/L, while total bilirubin (0.45 mg/dL) and direct bilirubin (0.16 mg/dL) remained within the normal range. The coagulation profile indicated a prolonged prothrombin time/international normalized ratio (PT/INR) of 1.71. Serum sodium was low at 127.8 mmol/L, suggesting hyponatremia. Alpha-fetoprotein levels were normal, with no biochemical indicators pointing towards hepatocellular carcinoma. Ultrasonography of the upper abdomen conducted on 29 June 2024 revealed a shrunken liver exhibiting coarse echotexture and wavy margins, findings that are consistent with established Liver Cirrhosis. The caliber of the portal vein was normal and no ascites were observed.

The diagnosis of liver cirrhosis in this patient was corroborated by both clinical history and investigative results. The prolonged history of cirrhosis dating back to 2012 suggested a chronic progression of liver disease. Ultrasonographic results revealed a shrunken liver with a coarse echotexture and irregular margins, which are typical structural characteristics of cirrhosis. Laboratory tests indicated elevated SGOT levels, implying ongoing hepatocellular damage, while bilirubin levels remained within the normal limits, signifying relatively preserved hepatic excretory function. Additionally, the identification of Grade II esophageal varices necessitating endoscopic band ligation indicates complications arising from portal hypertension. In summary, these clinical, laboratory and imaging findings collectively substantiate the diagnosis of chronic liver cirrhosis with complications related to portal hypertension.

Preparation of mesenchymal stem cells derived from adipose tissue

Human Allogeneic adipose-derived Stem Cells (AT-MSCs) were isolated from the stromal vascular fraction and expanded following the protocol by Gotze et al. with modifications to ensure Good Manufacturing Practice (GMP) compliance [20]. Briefly, we isolated Mesenchymal Stem Cells (MSCs) from healthy donor adipose tissue who were screened for infectious diseases, including HIV, cytomegalovirus, Epstein Barr virus, hepatitis A, hepatitis B, hepatitis C, syphilis and chlamydia. Adipose tissue was procured from a healthy volunteer *via* lipoaspiration under aseptic conditions in the operating room, following informed consent. About 100 mL of adipose tissue was collected in a sterile container and processed in a biosafety cabinet under sterile conditions. The adipose tissue underwent enzymatic digestion using collagenase type I and was incubated at 37°C with intermittent mixing. After digestion, the stromal vascular fraction was isolated through centrifugation and red blood cells were eliminated using a lysis buffer. The resulting cell pellet was washed and resuspended to create a single-cell suspension. The cells were cultured in DMEM/F12 medium enriched with fetal bovine serum and antibiotics at 37°C in a humidified environment containing 5% CO_2. Adherent mesenchymal stem cells were expanded and passaged up to Passage Three (P3). The cells were cryopreserved in liquid nitrogen using a dimethyl sulfoxide–based freezing medium until required. Before administration, MSCs were thawed, washed and resuspended in sterile normal saline.

Stem cell therapy and treatment protocol

The treatment was administered *via* Intravenous (IV) route, which was selected as the most effective method to guarantee systemic bioavailability and facilitate the efficient targeting of AT-MSCs to areas of liver damage. The IV administration was well tolerated, with no infusion-related complications noted during the procedure or in the following monitoring period. A total of 160 million viable MSCs were prepared for the complete therapeutic regimen. An initial dose of 50 million cells was given in each session scheduled for June 2024, July 2024 and October 2024, followed by a booster dose of 10 million cells in December 2025. The infusion procedures were carried out without any complications and the patient maintained hemodynamic stability throughout the process. No immediate or delayed adverse events were reported.

Outcome

The patient received treatment over a span of one year, with regular monitoring conducted on a monthly basis, encompassing both clinical evaluations and laboratory tests. The clinical assessments concentrated on fatigue, energy levels, appetite and overall physical health, while the biochemical analysis was primarily focused on bilirubin levels due to its importance in the progression and prognosis of liver disease. Throughout the treatment period, the patient reported consistent symptomatic improvements. Within the initial two weeks, she observed a decrease in fatigue, an enhanced appetite and increased energy, which enabled her to participate more actively in her daily routines. On December 6, 2025, the SGOT (17.4 U/L) and SGPT (10.2 U/L) levels were found to be within normal ranges and she conveyed that she felt "much lighter and more energetic" compared to her state before the treatment. Furthermore, no adverse events or complications were noted during the entire treatment and observation period, underscoring both the safety and effectiveness of the intervention.

Upon the conclusion of the stem cell therapy protocol, the patient exhibited clinical stabilization and an enhancement in overall well-being. During the follow-up assessment, there were no new occurrences of gastrointestinal bleeding, ascites or hepatic encephalopathy. Laboratory values remained stable without any further decline and no advancement of complications related to portal hypertension was noted. While follow-up imaging continued to reveal

morphological characteristics indicative of cirrhosis, there was an absence of radiological signs suggesting disease progression. This case not only illustrates the potential of intravenous MSC and exosome-based therapy in reversing hyperbilirubinemia and enhancing clinical status in patients with advanced liver cirrhosis but also highlights its potential as a feasible alternative to liver transplantation for select individuals.

Discussion

The patient exhibited clinical stabilization and an enhancement in overall well-being following the completion of allogeneic adipose tissue–derived mesenchymal stem cell therapy. During the follow-up period, there were no new occurrences of gastrointestinal bleeding, ascites or hepatic encephalopathy reported. Liver function tests and other laboratory parameters remained stable without any significant deterioration and no additional progression of complications related to portal hypertension was noted [21]. Although follow-up imaging continued to reveal morphological characteristics consistent with established liver cirrhosis, there was no radiological indication of further disease progression. Mesenchymal Stem Cells (MSCs) are regarded as a promising therapeutic option in regenerative medicine due to their high proliferative capacity, multilineage differentiation potential and immunomodulatory properties. According to the criteria established by the International Society for Cell & Gene Therapy, human MSCs must demonstrate adherence to plastic surfaces under standard culture conditions [22].

Cirrhosis, recognized as the most severe form of liver fibrosis, is marked by an overabundance of collagen accumulation and the development of regenerative nodules that disrupt the typical architecture of the liver [23]. Research has consistently demonstrated that Adipose Tissue-derived Mesenchymal Stem Cells (AT-MSCs) can ameliorate liver damage and fibrosis in experimental models induced by Carbon Tetrachloride (CCl4), thioacetamide and various other hepatotoxic substances [24]. In the aftermath of liver injury, resident macrophages secrete pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-1 and interleukin-6, which serve to attract immune cells and stimulate the activation of Hepatic Stellate Cells (HSCs). Following this, activated HSCs undergo transformation into myofibroblast-like cells that express α-Smooth Muscle Actin (α-SMA) and synthesize extracellular matrix proteins, such as Collagen type I Alpha 1 (Col1α1), thus playing a significant role in the progression of fibrosis. Moreover, activated HSCs produce Transforming Growth Factor-β1 (TGF-β1), which further enhances the fibrogenic process [25].

Multiple mechanisms have been suggested to elucidate the advantageous effects of mesenchymal stem cell therapy in the context of liver cirrhosis [26]. One potential mechanism involves the migration of MSCs to damaged liver tissue following systemic infusion, where they may differentiate into hepatocyte-like cells that express liver-specific markers such as CK7, CK19, albumin, FOXa2 and CX32. Conversely, another significant mechanism pertains to the paracrine functions of MSCs. Upon their migration to the injured liver tissue, AT-MSCs secrete a diverse array of cytokines, chemokines, growth factors and exosomes that play a role in tissue repair and the modulation of inflammation [27]. This repertoire includes interleukin-1 receptor antagonist, interleukin-6, interleukin-8, interleukin-10, monocyte chemoattractant protein-1, granulocyte colony-stimulating factor granulocyte-macrophage colony-stimulating factor bone morphogenetic protein-4, tumor necrosis factor-α, nerve growth factor Hepatocyte Growth Factor (HGF), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Insulin-like Growth Factor-1 (IGF-1) and Transforming Growth Factor-Beta (TGF-β).

Additionally, Mesenchymal Stem Cells (MSCs) can foster an immunologically tolerant milieu by facilitating the polarization of macrophages towards an anti-inflammatory state, transitioning them from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype [28]. This process effectively suppresses critical mediators associated with fibrosis, including TGF-β1, α-SMA and Col1α1, while also diminishing the activation of Hepatic Stellate Cells (HSCs). Furthermore, among the diverse array of growth factors released by MSCs, Hepatocyte Growth Factor (HGF) is particularly significant as it inhibits the activation of hepatic stellate cells, curtails collagen synthesis, induces apoptosis in activated myofibroblasts and boosts the activity of Matrix Metalloproteinases (MMPs). Similarly, Adipose Tissue-derived MSCs (AT-MSCs) may facilitate the degradation of the extracellular matrix by lowering the expression of Tissue Inhibitor of Metalloproteinase-1 (TIMP1) and enhancing MMP expression. Moreover, exosomal microRNAs, such as miR-122 and miR-181, have the potential to modulate gene expression in both hepatocytes and stellate cells, thereby supporting regeneration and minimizing scar formation. Additionally, growth factors like VEGF, HGF, EGF and IGF-1 can promote hepatocyte proliferation, angiogenesis, tissue repair and cell survival by upregulating anti-apoptotic pathways and inhibiting pro-apoptotic signaling [29].

Moreover, it has been demonstrated that MSCs can enhance liver function by elevating Albumin (ALB) concentrations and decreasing levels of hepatoenzymes such as alanine Aminotransferase (ALT), aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP). This indicates potential hepatoprotective and regenerative properties. Comparable positive outcomes have been noted in animal studies involving acute-on-chronic liver failure. Collectively, these regenerative, anti-inflammatory, immunomodulatory and anti-fibrotic processes may also explain the clinical stabilization, reduction in bilirubin levels, symptomatic improvement and absence of further disease progression observed in our patient.

Furthermore, earlier studies have indicated that allogeneic MSCT could lead to sustained clinical enhancements for as long as 2 years post-transplantation in individuals suffering from liver cirrhosis due to autoimmune disorders [30]. Consequently, while allogeneic AT-MSC therapy seems to be safe and might aid in the clinical improvement of liver cirrhosis for duration of up to 2 years following transplantation, it is essential to conduct more extensive long-term case-control studies and randomized controlled trials to validate its complete therapeutic efficacy. In general, the prognosis scores for the patient were notably lower (indicating improvement) during follow-up assessments compared to the baseline measurements. The patient was administered 50 million allogeneic AT-MSCs and did not receive a liver transplant throughout the treatment duration. Levels of CRP and leukocyte counts, which serve as indicators of potential systemic inflammation, were typically lower following treatment than at the baseline. Additionally, a gradual rise in albumin levels over time may also signify functional recovery. Collectively, these results imply that the administration of 50 million allogeneic AT-MSCs was safe, well-tolerated and may have played a role in the clinical improvement observed in this patient with liver cirrhosis.

Potential therapeutic mechanisms of MSCs in the treatment of cirrhosis

While cell therapy for cirrhosis has shown that MSCs can enhance liver function and provide positive outcomes regarding liver regeneration, the therapeutic mechanisms underlying these effects remain largely uncharacterized. Various mechanisms have been suggested through which these cells may aid in liver regeneration, such as their differentiation into hepatocytes, their fusion with native hepatocytes and a paracrine proliferative effect on hepatocytes [31,32]. Recently, numerous studies have highlighted the significant role of cell types beyond hepatocytes, including macrophages, hepatic stellate cells and lymphocytes, in the regulation of liver regeneration [33].

Furthermore, an imbalance in immune cell populations or the infiltration of immune cells into the liver can disturb the liver's immune-privileged status, potentially leading to liver injury or fibrosis. Increasing evidence suggests that the therapeutic mechanisms associated with MSC treatments are more clearly defined compared to those of BMCs or HSCs regarding liver regeneration. For example, MSCs have the capability to differentiate into hepatocyte-like cells both *in vitro* and *in vivo* and can release trophic factors, such as growth factors, cytokines and chemokines, which facilitate the regeneration of the damaged liver [34]. The trophic factors produced by MSCs are recognized not only for their ability to diminish inflammation, apoptosis and fibrosis in injured tissues but also for their role in promoting angiogenesis and tissue regeneration [35]. Additionally, trophic factors, including IL-10, hepatocyte growth factor transforming growth factor-beta 3 and tumor necrosis factor alpha secreted by MSCs, inhibit the proliferation of hepatic stellate cells and reduce collagen synthesis. Moreover, MSCs possess immune-modulatory capabilities and can migrate to sites of tissue damage. They are also capable of expressing various soluble factors, such as nitric oxide, prostaglandin E2, indoleamine 2,3-dioxygenase, IL-6, IL-10 and human leukocyte antigen G. These soluble factors play a crucial role in regulating the proliferation and functions of diverse immune cells and have been demonstrated to induce regulatory T cells.

Future Perspectives

For individuals suffering from cirrhosis, autologous Mesenchymal Stem Cells (MSCs) may serve as promising candidates for cell therapies aimed at enhancing the production of functional hepatocytes, which are essential for restoring impaired liver function. Nonetheless, it remains unclear whether these cells can effectively differentiate into hepatocytes *in vivo* at a clinically relevant and stable rate, as the trans-differentiation of MSCs into hepatocytes has not been frequently documented in animal studies [36]. Furthermore, distinguishing trans-differentiated hepatocytes from native hepatocytes in patients poses a significant challenge. Despite this, the positive effects of these cells have been noted in cirrhotic patients. Several pivotal aspects of clinical trials necessitate further exploration, including the ideal cell type for infusion, the most advantageous timing for therapy, the optimal quantity of cells, the preferred administration route and the best duration or frequency of injections. Prior to addressing these concerns, it is crucial to identify which specific types of cells within the bone marrow are chiefly responsible for liver regeneration. Emerging evidence suggests that resident stem cells within the bone marrow may have the capacity to differentiate into hepatocytes and enhance liver function. Among the various stem cell types, AT-MSCs are particularly amenable to isolation due to their plasticity and adhesive characteristics, allowing for sufficient expansion to meet clinical demands without compromising their stemness.

Additionally, the longevity of the engrafted cells is vital for achieving sustained therapeutic efficacy. In numerous pre-clinical animal studies, human cells have been tracked through immunohistochemical analysis utilizing human-specific markers; however, for successful clinical application, more advanced techniques will be necessary to accurately identify and monitor the trajectories of the injected cells [37]. For example, infused cells can be tagged with superparamagnetic iron oxide nanoparticles or reporter genes, enabling their tracking through advanced imaging technologies [38]. Anyhow, further studies are required to fully elucidate these mechanisms.

Conclusion

In summary, this case contributes to the expanding collection of evidence that endorses the application of AT-

MSC therapies as a potentially effective regenerative approach for individuals suffering from advanced liver cirrhosis. The noted decrease in SGOT and SGPT levels, along with symptomatic improvement, underscores the clinical significance of utilizing the AT-MSC secretome in the treatment of hepatic failure. Although liver transplantation is still considered the gold standard, our results suggest that AT-MSC interventions could serve as a feasible alternative or bridging therapy for patients who are either not suitable candidates for transplantation or are reluctant to pursue it. Further studies with higher numbers of patients are warranted to better clarify the impact and mechanisms of AT-MSCs in liver cirrhosis.

Conflicts of Interest

The authors declare no conflict of interest.

Consent

The patient and the volunteer, participating in the study, were informed about the procedures and their consent was obtained in advance.

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