A case report of congenital glycogen storage liver cirrhosis treated with bone marrow derived stem cells

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Abstract: Liver cirrhosis represents a state of end-stage failure that is usually fatal. The condition results in liver dysfunction, recurrent ascites, encephalopathy, renal failure, splenomegaly, bleeding, and a poor quality of life in general. With the current severe shortage of donated organs, the only available treatment in the developing countries remains palliative care. We report a case of congenital metabolic liver cirrhosis due to glycogen storage disease diagnosed at age eight. The patient, a male, received bone marrow derived mononuclear cells (BMMC) at age 16 and again at age 17 with significant improvement of his biochemical liver function tests, ascites build-up, asthenia, splenomegaly and quality of life. Furthermore, liver biopsies showed clear reduction of the inflammation and fibrosis from Ishak score dropped from 3 to 1 paralleling the symptomatic improvement of the patient.

Keywords: Mononuclear stem cells; liver cirrhosis; bone marrow cells

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Introduction

There are several causes of liver cirrhosis spanning autoimmune, viral, congenital, and toxic etiologies. Liver transplantation is the only potentially curative treatment for liver cirrhosis but is riddled with problems including the need for lifelong immune suppression and a long waiting period during which most patients expire especially in the developing countries. The high financial, medical and psychological costs make it out of reach for most patients (1-3). Many alternative approaches are being sought. One of those is cellular therapy; stem cells can be easily collected from the patient bone marrow or expanded ex vivo.

Glycogen storage disease consists of several conditions characterized by a transport defect of glucose-6-phosphate due to a mutation of one of the translocase enzymes. It usually results in neutrophil dysfunction and liver cirrhosis. The bone marrow mononuclear stem cells include several types of hematopoietic, mesenchymal and other precursor cells. There are several proposed mechanisms as to their mode of action. The cells usually home to the injured, inflamed areas as well as back to the bone marrow. Although the ultimate goal is to replace the defective cells by differentiation in a specific microenvironment, there is evidence of immune manipulation and paracrine activities that induce repair and reduce inflammation and fibrosis through several mediators (4-7).

The improvement is usually demonstrated by monitoring the liver function tests, the Child-Pugh and MELD scores, reduction in the ascites build-up, encephalopathy, and the quality of life (8-13).

Case presentation

Our patient is a 21-year-old man who was diagnosed with liver cirrhosis at age 8. At the time, he presented
with severe asthenia, very large ascites, failure to thrive and poor appetite. His liver function tests were elevated (Tables 1, 2), liver and spleen ultrasonography were compatible with liver cirrhosis. A liver biopsy showed significant triad inflammation, hepatocyte swelling and fibrosis compatible with glycogen storage disease stage 3 on the Ishak scoring system at the time. Since presentation, he was having paracentesis of about 6–8 liters every 5–6 days despite the use of diuretics. The serology for hepatitis A, B and C were negative on repeated occasions.

At age 16, after 3 days of 300 mcg of G-CSF priming given twice daily, 150 mL of bone marrow was aspirated from the posterior iliac crests using 6 portals with heparin sodium as anticoagulant under general anesthesia. The Bone Marrow was centrifuged and the supernatant fat cells and bone debris were removed.

In the Interventional Radiology Lab, the patient was prepped. Under local anesthesia, the right femoral artery was accessed using a Simon catheter advanced into the descending aorta up to the hepatic artery and the stem cells were infused over 15 minutes. The patient was observed for 24 hours following the procedure.

Following the infusion of the stem cells, the ascites build-up became 2–4 liters every 20–30 days on the average. At age 17, a second infusion of bone marrow derived stem cells was performed again in the Hepatic artery. Following this procedure, the ascites diminished gradually over the following 3 months until no paracentesis was necessary and a very small residue could be detected by ultrasonography with no need for any diuretics or taping.

The patient tolerated the procedures well with no major complications or other effects. No bleeding, hemodynamic instabilities, infectious or other adverse events were reported over the last 4 years of follow up. The blood counts varied slightly after the procedure but no significant cytopenias were noted. The duration of response has been significant and longer than reported in the literature (12-14). The diuretic requirements of spironolactone and furosemide were variable but mostly high before the procedure and diminished gradually until they were stopped about 3 months following the procedure. A liver biopsy was taken 2 years following the procedure (Figures 1, 2) and reviewed by two independent pathologists, it showed again stigmata of hepatocyte swelling, sinus congestion, portal inflammation and fibrosis, however, this was significantly improved compared to the pre-treatment biopsy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
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<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
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<tr>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>Creatinine (mg/L)</td>
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</tr>
<tr>
<td>INR</td>
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<tr>
<td>Albumin (g/dL)</td>
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<tr>
<td>Ascites score</td>
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</tr>
<tr>
<td>Encephalopathy</td>
<td>No</td>
</tr>
<tr>
<td>Spleen size (cm)</td>
<td>17</td>
</tr>
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INR, international normalization ratio.

<table>
<thead>
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<th>Variables</th>
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<tbody>
<tr>
<td>MELD score</td>
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<tr>
<td></td>
<td>12.4</td>
</tr>
<tr>
<td>Child score</td>
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<tr>
<td>Child Pugh score</td>
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description. The Ishak liver fibrosis score was downgraded to 1 compared to 3 before the procedures (Figures 3,4). The patient has been on the liver transplant waiting list in the area and is considered stable since.

**Discussion**

Over the past decade, significant evidence accumulated showing the safety and efficacy of cell therapy in the treatment of liver cirrhosis (7-13). Our case adds one more piece of evidence to show that the bone marrow derived cells given to patients with liver cirrhosis may improve the Child and MELD scores as well as the biochemical tests, and most importantly, the quality of life of the patient correlating with the pathologic improvement. Repeated injections may add up the beneficial effects even though the optimal sequence and schedule is not known (8-12).

This is the first case report showing pathologic evidence along with improvement of the clinical picture of the disease even though one has to keep in mind that many more cases and randomized studies are needed to confirm and verify these results. It is difficult to explain how the autologous cells which carry the same congenital mutations could help a congenital problem except by compensatory and paracrine routes resulting in reduction of the fibrosis. The stem cells have been postulated to regulate the immune cytokines and growth factors to control the liver matrix secreting cells and therefore the process of fibrosis (15-17).

Liao et al. reported giving autologous bone marrow cells to 12 patients with post-hepatitis cirrhosis and portal hypertension through the hepatic artery after *in vitro* expansion for 7 days. They reported improvement of the liver function tests and stabilization of the liver-related symptoms over the following 6 months (12). Al Tayeb et al. showed efficacy and safety of autologous stem cell transplantation in patients with liver cirrhosis related to hepatitis C infections (13). Yannaki et al. proved the safety and efficacy of mobilized peripheral blood stem cells (PBSCs)
in patients with advanced-stage alcoholic liver cirrhosis (14).

In addition to the bone marrow derived stem cells, several groups have studied autologous and allogeneic mesenchymal stem cells (MSCs) and reported positive results (10,18-20). Zhang et al. reported a significant reduction of the volume of ascites and improved liver function tests, albumin, and bilirubin in 30 patients treated with Umbilical cord-derived allogeneic MSCs compared with 15 patients treated with saline as controls (18).

El-Ansary reported on 25 patients with advanced (Child C) liver cirrhosis treated with autologous bone marrow-derived MSCs in patients with chronic hepatitis C infection. Partial objective improvement of liver function tests, prothrombin time, albumin, bilirubin and MELD score were reported (21).

Conclusions

We hope that well designed, large, randomized studies will prove the best types, methods and schedules to get the most out of the stem cells in the future.

In our case, the pathologic proof and improvement of the albumin manufacturing, prothrombin time, liver function tests, splenomegaly, and rate of ascites production and build up are surrogate measures that can be used to assess the effects on patients (19).

It is unclear which pathologies and etiologies may benefit more from this treatment and whether this improvement could serve as a bridge to hold the patients long enough until liver transplants become available or even unnecessary.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

References


