Graft Versus Host Disease

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Abstract
Graft Versus Host Disease (GVHD) is a rare complication of liver transplantation with a mortality rate exceeding 65%. A 53-year-old male presented with a diffuse maculopapular rash, diarrhea, lymphopenia, fever, and confusion 14 days after orthotopic liver transplantation for hepatitis B cirrhosis. Skin biopsy and HLA-typing of peripheral blood confirmed a diagnosis of solid organ transplant related GVHD. This report summarizes what is known about this disease and emphasizes the importance of early diagnosis, which is one of the only factors known to improve the mortality of this deadly condition.

Résumé
La réaction du greffon contre l’hôte (Graft Versus Host Disease ou GvHD) est une complication plutôt rare de la greffe de foie. Le taux de mortalité lié à cette affection dépasse les 65 %. Nous décrivons ici le cas d’un homme de 53 ans qui, 14 jours après avoir subi une greffe hépatique orthotopique pour une cirrhose due à l’hépatite B, présente une éruption maculopapuleuse diffuse, de la diarrhée, une lymphopénie, de la fièvre et de la confusion. Une biopsie cutanée et le typage-HLA du sang périphérique ont confirmé un diagnostic de réaction du greffon contre l’hôte consécutive à la greffe d’un organe solide. Ce rapport fait un résumé de ce que l’on connait de cette maladie mortelle et met l’accent sur l’importance d’un diagnostic précoce, qui est l’un des seuls facteurs connus pouvant améliorer l’issue de cette condition mortelle.
Case Presentation

A 53-year-old previously healthy male underwent orthotopic liver transplantation for hepatitis B cirrhosis. At the time of transplantation, he had a Model for End stage Liver Disease (MELD) score of 22.

The surgery was uneventful and his postoperative course was unremarkable. The patient was transferred out of the Intensive Care Unit without issue. The Immunosuppressive regimen consisted of one dose of antithymocyte globulin (ATG), two doses of the monoclonal antibody basiliximab, as well as daily methylprednisolone, mycophenolate mofetil (MMF), and tacrolimus.

On Post-Operative Day (POD) 10, the patient developed confusion and asterixis, and was treated with Lactulose for presumed hepatic encephalopathy. On POD 14, the patient’s lymphocyte count decreased, and prednisone and MMF doses were reduced. On POD 16, the patient developed right-sided abdominal pain, diffuse watery diarrhea, and a headache. Prednisone and MMF doses were decreased further. On POD 18 the patient developed a rapidly progressive diffuse maculopapular rash involving the trunk, and extremities (Figure 1). Given that a drug reaction was considered as a possible etiology of this rash, Septra and Valgancyclovir were discontinued. One day later, the patient developed a fever of 38.6°C and was started empirically on piperacillin-tazobactam.

The patient then developed progressive confusion, tachypnea (respiratory rate 28 breaths per minute), tachycardia (heart rate 116 beats per minute), hypotension (BP 77/47 mmHg), and worsening confusion. On POD 23, the patient was admitted to the Intensive Care Unit (ICU).

Initial investigations in the ICU showed hemoglobin 91 g/L, platelet count 32 x 10⁹/L, white blood cell (WBC) count 0.59 x 10⁹/L (neutrophils 0.49 x 10⁹/L), creatinine 76 μmol/L, ALT 15 U/L, ALP 53 U/L, conjugated bilirubin 11 μmol/L, INR 1.09, and Albumin 19 g/L. Computed tomography showed moderate airspace disease in the lower lobes of the lungs bilaterally and diffuse dilatation of the small and large bowel.

The patient was volume resuscitated, intubated for respiratory distress, and Piperacillin-Tazobactam was replaced by Imipenem and Vancomycin. In addition, stress doses of steroids were given. Differential diagnosis at this time included acute Graft Versus Host Disease (GVHD), Toxic Epidermal Necrolysis (TEN), viral infection such as Cytomegalovirus (CMV), organ rejection, sepsis, or adrenal insufficiency.

Further investigations demonstrated negative CMV IgM and PCR, negative Parvovirus B19 IgG and IgM, a random cortisol level of 487 mmol/L, and negative stool cultures. Blood and sputum cultures were positive for Vancomycin Resistant Enterococcus (VRE) and skin biopsy revealed acute interface dermatitis, vacuolar type, with necrotic keratinocytes and no evidence of eosinophils, which was most suspicious of acute GVHD. Human Leukocyte Antigen (HLA) typing of peripheral blood and the patient’s oral cavity demonstrated 85% donor lymphocytes, confirming this diagnosis.

Discussion

This case presentation describes a typical presentation of an uncommon disease. Although GVHD is a common occurrence following Hematopoietic Stem Cell Transplantation (HSCT), it is a rare complication after solid organ transplantation, with an incidence of 1-2%.¹

Billingham et al. first described the prerequisites needed for the development of GVHD from any cause in 1966.² First, a source of immunocompetent lymphocytes must be introduced into a host. It has been demonstrated that between 10⁷ to 10⁸ donor lymphocytes are stored in the portal tract and parenchyma of transplanted livers.³ Next, there must be differences between the histocompatibility antigens of donor lymphocytes and host cells which occurs following liver transplantation because, unlike in the HSCT population, recipients of organ transplantation are not Human Leukocyte Antigen (HLA) matched with the donor organ. Lastly, the host must be unable to reject the HLA unmatched donor.

Figure 1
Table 1: Differential Diagnosis and Differentiating Features of GVHD after Liver Transplantation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CMV</th>
<th>TEN</th>
<th>Rejection</th>
<th>Sepsis</th>
<th>GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rash</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes/No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Confusion</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>↑/→</td>
<td>→</td>
<td>↑</td>
<td>↑/→</td>
<td>→</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Biopsy</td>
<td>Biopsy</td>
<td>Biopsy</td>
<td>Clinical</td>
<td>Biopsy</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, Cytomegalovirus; TEN, Toxic Epidermal Necrolysis; GVHD, Graft Versus Host Disease.

Table 2: Clinical Features of GVHD after Liver Transplantation

<table>
<thead>
<tr>
<th>Clinical Features of GVHD After Liver Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash (involves palms/soles)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Normal liver enzymes and liver function</td>
</tr>
</tbody>
</table>

lymphocytes, which occurs following liver transplantation due to the multiple immunosuppressive medications used to prevent rejection.

Much like in the HSCT population, GVHD following liver transplantation is characterized by a maculopapular rash involving the palms and soles (94.2%), fever (66.6%), diarrhea (54%), and pancytopenia (54%) (Table 2). It usually occurs between 2 to 8 weeks post-operatively. However, unlike in the HSCT population, liver transplant related GVHD typically does not affect the liver because graft lymphocytes actually originated from this organ, making it an immune-tolerated site.

A skin biopsy that demonstrates epidermal dyskeratosis and epithelial cell necrosis is very suggestive of GVHD but is not diagnostic. To confirm a diagnosis in solid organ transplant associated GVHD, chimerism, the presence of donor cells in the host’s blood or tissues, must be demonstrated.

A large retrospective study published in 2007 by Chan et al. looked at 205 patients from a large database who had received a liver transplantation and compared those patients who developed GVHD (1.9%) with those who did not. Although the number of GVHD cases was very small, the authors identified that patients with autoimmune hepatitis (AIH), alcoholic liver disease (ALD), and hepatocellular carcinoma (HCC) were significantly more likely to develop GVHD (with an incidence of GVHD in these populations of 16%, 5.6% and 7.1% respectively). In addition, patients with GVHD were significantly more likely to have diabetes mellitus (DM) than those patients who did not develop the disease (p=0.02). These authors suggest that because DM, AIH, and HCC are immunodeficient states, patients with these conditions are more likely to fail to destroy donor lymphocytes introduced during liver transplantation.

Another retrospective study published in 2005 by Kamei et al. determined the degree of mismatch at the HLA –A, –B, and –DR loci between the donors and recipients of all liver transplants performed in Japan. They identified 906 pairs of patients, 8 of whom developed GVHD. They found that all patients that developed GVHD had one-way donor-dominant HLA matching at all three of these alleles. This means that at all 3 loci, the recipient was heterozygous and the donor was homozygous for an identical allele. This combination is thought to contribute to the development of GVHD because it renders the recipient unable to recognize the donor lymphocytes as foreign early after transplantation. Donor lymphocytes are then able to proliferate, undetected by the host’s immune system and attack host tissues.

Unfortunately, although multiple treatment modalities have been attempted, the mortality rate of GVHD following liver transplantation exceeds 65%. Multiple approaches, including decreasing immunosuppressive therapy to enable the host immune system to kill the donor lymphocytes, as well as increasing immunosuppression to suppress the damaging activities of activated donor lymphocytes have been tried with little success. Unfortunately, no individual medication or combination of medications has proven effective at altering the mortality rate of this disease. Commonly used approaches include the use of corticosteroids, the anti T cell antibodies ATG and alemtuzumab (Campath), the cytokine inhibitors infliximab and entanercept, immunoglobulins, antimetabolites such as azathioprine, and alkylating agents such as cyclophosphamide.

A recent review article by Akbulut et al. analyzed all 87 case reports of GVHD after liver transplantation in the literature and determined that factors that are significantly associated
with higher mortality include the presence of pancytopenia, diarrhea, a larger age difference between the recipient and donor, and an increased time from symptom onset to diagnosis and treatment.  

Further research into the possible risk factors of this condition may help to decrease the incidence of this disease. Interventions that may reduce the development of GVHD after liver transplantation include avoiding one-way donor-dominant HLA mismatch and treating the liver specimen with anti-lymphocyte preparations prior to transplant in patients with certain etiologies of liver disease, such as AIH, ALD, and HCC. To date, there has been no clear pattern of success in regards to choosing a treatment modality, and this will be an area of active research in the future. 

In the case of the patient described here, after acute transplant-related GVHD was confirmed with HLA typing of peripheral blood, the patient was treated with high doses of corticosteroids and the anti T cell antibodies ATG and Alemtuzumab. After discontinuation of tacrolimus, cyclosporine was continued throughout this treatment regimen. 

Unfortunately, the patient developed progressive multi-organ dysfunction and passed away of sepsis and invasive aspergillus on POD 45. 

Although GVHD is a rare complication after liver transplantation, physicians should recognize the classical presenting symptoms and signs of this disease, which include diarrhea, confusion, a maculopapular rash involving the palms and soles, pancytopenia and the absence of liver enzyme elevations. Due to the non-specific nature of these presenting features, it is important to consider GVHD early on in transplant patients presenting with some or all of these symptoms. Although multiple treatment regimens have been tried, due to the complicated interactions between the host and donor immune systems, there is currently no known effective treatment for this disease and the mortality rate continues to exceed 65%. Early diagnosis is crucial as this is one of the only factors known to significantly improve the mortality of this deadly condition.

References

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