Fulminant liver failure due to severe veno-occlusive disease after haematopoietic cell transplantation: a depressing experience

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Summary

Background: Between 1988 and 2002, eight patients were referred to our unit from other institutions, for management of fulminant hepatic failure (FHF) complicating severe veno-occlusive disease (VOD).
Aim: To review our experience with these patients.
Methods: Retrospective analysis of medical case notes.
Results: In 7/8 cases, a histological diagnosis of VOD was confirmed by transjugular liver biopsy or post-mortem examination. All had undergone high-dose chemotherapy. Cyclophosphamide was included in the conditioning regimen of six patients. All developed encephalopathy and four progressed to grade 3 or 4 encephalopathy. All patients died, none surviving >75 days after haematopoietic cell transplantation. Three were listed for liver transplantation: one underwent transplantation, and two died before transplantation could be performed. Two suffered significant complications of transjugular liver biopsy. One underwent transjugular intra-hepatic porto-systemic venous stent (TIPS) insertion.
Discussion: FHF complicating severe VOD is associated with multi-organ failure, and has a very poor prognosis. Our experience and that described in published literature, questions the benefits of measures such as liver transplantation or prolonged intensive care.

Introduction

Veno-occlusive disease was unwittingly first described in South Africa in the 1920s, secondary to senecio poisoning. Early descriptions of ‘Chiari’s syndrome’, caused by the ingestion of medicinal teas containing pyrrolizidine alkaloids such as that found in the plant species Senicio, were uncommon. It was not until the 1950s that the term ‘hepatic veno-occlusive disease (VOD)’ was used to describe non-thrombotic, fibrous obliteratorative endophlebitis of small centrilobular hepatic venules. With the introduction of myeloablative chemotherapy induction protocols in bone marrow transplantation, VOD became well recognized. There are a large number of chemotherapeutic agents associated with VOD; high-dose cyclophosphamide and azathioprine are commonly implicated. More recently, the term ‘sinusoidal obstruction syndrome’ (SOS) has been proposed to replace the term VOD, as it has been suggested that SOS more accurately reflects the nature of the toxic injury to hepatic sinusoids. While the occlusion of the central veins is easily recognizable, prompting the original description of VOD, it is not essential for the diagnosis.

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The incidence of VOD following haematopoietic cell transplantation is as high as 54% in regimens using high-dose cyclophosphamide and total body irradiation. Prognosis is variable, with mortality rates ranging from 7% to 50%. Severe VOD is the third leading cause of transplant-related death in allogeneic bone marrow transplantation. The major prevention strategy for VOD in the setting of haematopoietic cell transplantation is to identify high-risk patients prior to cytoreductive therapy, and to use low-risk regimens. The presence of HCV infection, non-alcoholic steatohepatitis, systemic infection, and the use of busulphan and cyclophosphamide in myeloablative regimens, increases the risk of fatal VOD.

The incidence of VOD has fallen in recent years, due to: (i) the use of non-myeloablative chemotherapy and the avoidance of high-dose cyclophosphamide in preconditioning regimens; (ii) the more careful use of busulphan, including drug monitoring in some centres; (iii) identification of high-risk patients by screening of liver function tests prior to initiation of myeloablative therapy; and (iv) the appropriate monitoring of cyclosporin levels, thus reducing the incidence of cyclosporin toxicity (which can mimic VOD). The use of ursodeoxycholic acid (UDCA) prophylaxis has been proposed by some centres to reduce the risk of developing VOD, although more recent data suggests it has no effect.

VOD is classified as mild, moderate or severe disease. A model for predicting fatal outcome of VOD after bone marrow transplant has been developed. The rapidity of serum bilirubin rise and weight gain during the first 2 weeks post cyclophosphamide-based conditioning are the most important predictors of clinical outcome.

Mild cases of VOD, though clinically obvious, require no specific treatment and resolve completely. Moderate cases have clinical signs which require symptomatic treatment with diuretics, analgesics and paracentesis, but generally resolve within 100 days. Severe VOD, occurring in approximately 25% of cases, does not resolve before 100 days and is associated with a very poor prognosis. This represents a major clinical challenge for the practicing physician. Indeed, it has been suggested that mechanical ventilation is futile in patients with severe VOD complicated by multi-organ failure.

We have reviewed the experience of the Birmingham Queen Elizabeth Hospital Liver Unit in the management of patients with fulminant hepatic failure consequent to severe VOD.

Case histories

Eight patients were referred from other institutions between 1988 and 2002 with severe VOD complicated by FHF. All had undergone high-dose chemotherapy, with 6/8 including cyclophosphamide in the conditioning regimen. Table 1 details the cytoreductive therapy used, as well as the clinical and biochemical features of each patient. All patients had clinical features consistent with fulminant VOD (defined as the presence of at least grade 1 hepatic encephalopathy). Four patients progressed to grade 3 or 4 encephalopathy requiring mechanical ventilation. Only one patient received prophylaxis against VOD. Table 2 details the treatment given for each patient. Three were listed for liver transplantation, but only one patient underwent transplantation. The other two died prior to transplantation. For seven patients, a histological diagnosis of VOD was confirmed either by transjugular liver biopsy (TJB) or at post-mortem examination. Unfortunately, all patients died, and none survived more than 75 days after haematopoietic cell transplantation. Two patients experienced significant complications of transjugular liver biopsy (TJB).

Patient 1

A 24-year-old female underwent autologous PBSCT (day 0) for nodular sclerosing Hodgkin’s disease (stage IIB). The conditioning regimen included cyclophosphamide, busulphan and TBI. Seventeen days following BMT (day 19) jaundice, peripheral oedema, ascites and tender hepatomegaly were noted. On day 22, encephalopathy developed. Following transfer to the Birmingham Liver Unit, TJB was undertaken and confirmed the diagnosis of acute VOD (severe centrilobular congestion with sinusoidal dilatation and perivenular hepatocyte loss). The patient was listed for liver transplantation. Unfortunately, the following day the patient deteriorated rapidly and died. Post-mortem examination found a liver capsular tear and 3 l of blood in the peritoneum.

Patient 2

A 24-year-old male underwent allogeneic BMT (day 0) for Philadelphia-positive chronic myeloid leukaemia. The conditioning regimen included cyclophosphamide, busulphan and TBI. Nineteen days following BMT (day 19) jaundice, peripheral oedema, ascites and tender hepatomegaly were noted. On day 22, encephalopathy developed. Following transfer to the Birmingham Liver Unit, TJB was undertaken and confirmed the diagnosis of acute VOD (severe centrilobular congestion with sinusoidal dilatation and perivenular hepatocyte loss). The patient was listed for liver transplantation. Unfortunately, the following day the patient deteriorated rapidly and died. Post-mortem examination found a liver capsular tear and 3 l of blood in the peritoneum.
Table 1  Clinical and biochemical characteristics of eight patients referred to the Birmingham Liver Unit between 1988 and 2002

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Year</th>
<th>Cancer diagnosis</th>
<th>Haematopoietic transplantation</th>
<th>Cytoreductive therapy</th>
<th>Time to liver failure*</th>
<th>Creatinine (μmol/l)</th>
<th>Bilirubin (μmol/l)</th>
<th>AST (U/l)</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>F</td>
<td>1988</td>
<td>Chronic myeloid leukaemia</td>
<td>Allogenic BMT</td>
<td>Cyclophosphamide, Busulphan, TBI</td>
<td>22</td>
<td>482</td>
<td>966</td>
<td>210</td>
<td>2.4</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>F</td>
<td>1994</td>
<td>Acute myeloid leukaemia</td>
<td>Planned allogenic BMT**</td>
<td>Atra, daunorubicin, cytarabine, etoposide</td>
<td>31</td>
<td>130</td>
<td>116</td>
<td>5810</td>
<td>4.8</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>F</td>
<td>1996</td>
<td>Carcinoma breast</td>
<td>Autologous PBSCT</td>
<td>Cyclophosphamide</td>
<td>11</td>
<td>366</td>
<td>421</td>
<td>4453</td>
<td>11.2</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>F</td>
<td>1997</td>
<td>Carcinoma breast</td>
<td>Autologous PBSCT</td>
<td>Cyclophosphamide</td>
<td>34</td>
<td>200</td>
<td>1035</td>
<td>6085</td>
<td>1.8</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>M</td>
<td>1998</td>
<td>Multiple myeloma</td>
<td>Allogenic PBSCT</td>
<td>Melphalan, TBI</td>
<td>20</td>
<td>492</td>
<td>459</td>
<td>2541</td>
<td>4.3</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>F</td>
<td>2002</td>
<td>Chronic myeloid leukaemia</td>
<td>Allogenic PBSCT</td>
<td>Cyclophosphamide, Busulphan</td>
<td>20</td>
<td>280</td>
<td>1135</td>
<td>2012</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Laboratory features given refer to the maximum value recorded during each patient’s illness. BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; TBI, total body irradiation. *Time (days) to development of hepatic encephalopathy following haematopoietic cell transplantation (day 0). **See case history.
haemofiltration were initiated. Tissue plasminogen activator (TPA) therapy was given on day 19. Despite supportive care, the patient died of multi-organ failure on day 21. Post-mortem examination revealed a congested liver and histology diagnostic of acute VOD (zone 2 and 3 haemorrhagic necrosis and centrilobular venous occlusion by loose fibrous tissue, intimal cells and erythrocytes). Pulmonary haemorrhage and residual haematological disease were noted in the mediastinum.

**Patient 3**

A 49-year-old male underwent an autologous PBSCT for Stage IVB B-cell high-grade non-Hodgkin’s lymphoma. The conditioning regimen included cyclophosphamide and busulphan. Thirty-one days following PBSCT (day 31), jaundice, ascites and encephalopathy were noted. On arrival at the Liver Unit, the patient was intubated and ventilated (day 40). Hepatic venography confirmed patency of the hepatic veins, and a TJB confirmed the diagnosis of acute VOD (day 41). The patient underwent liver transplantation on day 43. Histological examination of the explanted liver was compatible with the TJB, and confirmed severe acute VOD. Following transplantation there was persistent multiple organ failure, and the patient died, 74 days after PBSCT and 31 days after liver transplantation.

**Patient 4**

A 21-year-old female was admitted for a planned allogenic BMT to treat her relapsed acute myeloid leukaemia (type M3). The conditioning regimen included Atra, daunorubicin, cytarabine and etoposide. At the time her chemotherapy was started, the patient was receiving a course of antibiotics for a positive Hickman line culture. Three days later the patient was noted to be breathless, and an echocardiogram demonstrated the presence of a severe dilated cardiomyopathy, possibly related to previously administered adriamycin. Thirty days later, the patient was noted to be jaundiced with associated weight gain and tender hepatomegaly. Within 24 h, TPA therapy was initiated for a presumed diagnosis of VOD. The same day, the patient became profoundly encephalopathic, and was intubated and ventilated. A TJB was performed 48 h later. As a consequence of a thromosed right-sided jugular vein, the TJB was performed via a left-sided approach. At the time of the TJB, it was noted that cardiac perforation had occurred. The patient underwent urgent pericardiocentesis, with haemodynamic improvement. However, there was continued deterioration and renal failure. The patient died with multiple organ failure the following day. Histology confirmed ischaemic necrosis and congestion in the zone 2 and 3 liver acinus, consistent with acute VOD.

**Patient 5**

A 44-year-old female underwent autologous PBSCT for carcinoma of the breast. The conditioning regimen included high-dose cyclophosphamide. Ten days later (day 10), peripheral oedema, ascites, jaundice and significant weight gain were noted. On arrival to the Liver Unit the patient was noted to be profoundly encephalopathic, and was intubated and ventilated (day 11). N-acetyl cysteine therapy was initiated. Emergency transjugular intrahepatic porto-systemic shunts (TIPS) was performed on day 11. TPA therapy was administered on day 12. The patient developed escalating noradrenaline requirements and died on day 13. Post-mortem examination

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**Table 2** Treatment characteristics and outcome of eight patients referred to the Birmingham Liver Unit between 1988 and 2002

<table>
<thead>
<tr>
<th>Patient</th>
<th>Transjugular liver biopsy (TJB)</th>
<th>Cause of death</th>
<th>Complications post TJB</th>
<th>Mechanical ventilation</th>
<th>Artificial renal support</th>
<th>VOD-specific treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Terminal anaemia</td>
<td>Liver capsular tear</td>
<td>No</td>
<td>Yes</td>
<td>Listed for OLTx</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>Multi-organ failure</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>TPA</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Multi-organ failure</td>
<td>Nil</td>
<td>Yes</td>
<td>Yes</td>
<td>OLTx</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Cardiomyopathy</td>
<td>Cardiac perforation</td>
<td>Yes</td>
<td>No</td>
<td>TPA</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>Multi-organ failure</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>TIPS, TPA, NAC</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Multi-organ failure</td>
<td>Nil</td>
<td>No</td>
<td>Yes</td>
<td>TPA, heparin</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Respiratory failure/sepsis</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>Listed for OLTx</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Respiratory failure/sepsis</td>
<td>Nil</td>
<td>Yes</td>
<td>No</td>
<td>Defibrotide, URSO, NAC</td>
</tr>
</tbody>
</table>

NA, not appropriate; OLTx, orthotopic liver transplantation; TPA, tissue plasminogen activator; NAC, N-acetyl cysteine, TIPS, transjugular intrahepatic porto-systemic shunts; URSO, ursodeoxycholic acid.
revealed extensive zonal necrosis of zones 2 and 3 of the liver acinus, with terminal hepatic venule congestion and occlusion consistent with acute severe VOD.

**Patient 6**
A 52-year-old female underwent autologous PBSCT for carcinoma of the breast. The conditioning regimen included high-dose cyclophosphamide. Eight days later (day 8) jaundice, ascites and renal impairment were noted. TPA therapy and low-dose heparin were administered for 5 consecutive days, with some clinical improvement. The patient self-discharged from the local hospital, but was readmitted with grade 1 encephalopathy on day 34, then transferred to the Birmingham Liver Unit. TJB performed on day 38 confirmed the diagnosis of acute VOD. The patient's condition failed to improve with conservative care. She suffered significant ascites but declined further treatment. According to her wishes, she was discharged home (day 42) and she died 2 weeks later.

**Patient 7**
A 38-year-old male underwent allogeneic PBSCT for stage IIIA non-secretory multiple myeloma. The conditioning regimen included melphalan and TBI. Fourteen days after PBSCT (day 14) jaundice, ascites, tender hepatomegaly and renal impairment were noted. A clinical diagnosis of VOD was made. Ultrasound imaging of the liver revealed ascites, hepatomegaly and patent vessels with reverse flow in the portal vein. Intermittent haemodialysis was commenced. On arrival at the Liver Unit, the patient was profoundly encephalopathic with respiratory failure, and was intubated and ventilated (day 20). The patient was listed for liver transplantation. There was prompt clinical deterioration, and the patient died on the waiting list (day 22). Post-mortem examination was refused by the patient's family.

**Patient 8**
A 36-year-old female underwent allogeneic PBSCT for accelerated-phase chronic myeloid leukaemia in remission. The conditioning regimen included cyclophosphamide and busulphan. The patient received UDCA prophylaxis for VOD. Fifteen days after PBSCT (day 15), ascites and a tender hepatomegaly were noted. On day 18, defibrotide therapy was started (30 mg/kg in four divided doses increased to 40 mg/kg after two doses). On day 19, significant renal dysfunction was noted. On arrival at the Liver Unit, the patient was commenced on haemofiltration (day 20). UDCA treatment was maintained and N-acetyl cysteine therapy was initiated the following day. TJB (day 35) confirmed the diagnosis of acute VOD. Despite continued medical therapy, the patient developed worsening sepsis and respiratory failure, and it was decided that mechanical ventilation would be futile. The patient died on day 54.

**Discussion**
The diagnosis of VOD following myeloablative chemotherapy can be made using simple clinical criteria, although these may not be particularly sensitive. Serum bilirubin, AST and ALT levels may be markedly elevated in fulminant VOD as was evident in our study.

Where diagnostic uncertainty remains, a liver biopsy is helpful. Transjugular liver biopsy (TJB) is therefore commonly used, with the added advantage of demonstrating elevated hepatic venous pressure gradients. Biopsy is highly specific for VOD, and effectively excludes a diagnosis of acute graft vs. host disease, an important differential diagnosis. The transjugular method may reduce the risk for haemorrhagic complications. However, even with transjugular liver biopsy, significant bleeding can occur. We observed two serious complications of TJB.

Early histological changes in VOD demonstrate haemorrhage, subendothelial oedema into the space of Disse, and damage to the central vein endothelium. The resultant centrilobular coagulative necrosis involves predominantly zone 3 liver acinus, with the severity and number of such histological changes correlating with the clinical syndrome. Histological changes observed for our cohort with severe VOD frequently included changes extending from zone 3 into zone 2 of the liver acinus. Late histological changes in VOD see the nature of the circulatory obstruction result from sinusoidal fibrosis.

It has recently been shown that increased exposure to toxic metabolites of cyclophosphamide (area under the curve analysis) is associated with increased liver toxicity and non-relapse mortality after haematopoietic cell transplantation. Six of eight patients in our cohort with fulminant liver failure had received high-dose cyclophosphamide as part of their preconditioning regimen. The avoidance of cyclophosphamide-based regimens in high-risk patients therefore seems prudent. Busulfan is another cytotoxic drug for which a relationship between exposure and the toxicity of the conditioning regimen has been observed.

With busulfan-based myeloablative regimens, both
early- and late-onset VOD can occur. Adjustment of busulphan dosing (based on plasma concentrations) in high-risk patients may become routine clinical practice.

Prophylactic pharmacological approaches have been tried, with variable success. Anticoagulation with low-dose intravenous heparin appears not to be beneficial in the prevention of VOD, although low-molecular-mass heparin prophylaxis may be of some benefit, and warrants further investigation. Prophylactic UDCA (a hydrophilic, non-hepatotoxic bile salt) reduced the severity of post-transplantation VOD in two published randomized controlled trials. Only one patient referred to transplantation VOD in two published randomized controlled trials.

Experimental evidence suggests that glutamine and glutathione supplementation may protect hepatocellular function in significant hepatic injury. In vitro, cytotoxic drugs that cause VOD target sinusoidal endothelial cells, which in turn appear more susceptible to profound glutathione depletion and injury than hepatocytes. To date, no clinical trials have examined whether prophylactic administration of glutathione supplements such as N-acetyl cysteine or methionine reduces the incidence of fatal VOD post haematopoietic cell transplantation. There are theoretical concerns that such drugs may have the potential to provide tumour protection. However, the use of N-acetyl cysteine at 50–150 mg/kg/day for 2–4 weeks as a treatment for VOD was associated with improvement in liver function and inflammatory markers in three patients, although it is difficult to know to what extent these patients would have improved spontaneously without therapy. In the Birmingham experience, the use of N-acetyl cysteine for the treatment of fulminant VOD in two patients did not appear beneficial.

The majority of patients with mild to moderate VOD recover spontaneously. Severe VOD remains a therapeutic challenge. In particular, attempts at preventing the development of multi-organ failure are paramount, as they are associated with a near-100% mortality. Various treatment strategies have been tried, with limited success.

Thrombolytic therapy with tissue plasminogen activator (TPA) and heparin infusions may be of benefit in the absence of associated renal or respiratory failure. However, there is the risk of life-threatening bleeding in patients treated with thrombolytics for VOD. No clinical benefit from the use of TPA was observed in four patients from our cohort.

Defibrotide is a single-stranded deoxyribonucleic acid with anti-thrombotic, anti-ischaemic and thrombolytic properties at the microvascular level. Initial reports of the use of defibrotide for severe VOD (at doses of 25 mg/kg/day) were promising. Recently, defibrotide has been demonstrated to improve the outcome of severe VOD associated with multi-organ failure in a multi-institutional study involving 88 patients. While this study was not randomized or controlled, it does suggest that defibrotide is beneficial in the treatment of severe VOD, with very little in the way of significant side-effects. It is anticipated that defibrotide will come into use routine clinical use for the treatment of moderate to severe VOD with or without multi-organ failure. Defibrotide is also a promising agent in the treatment of VOD developing secondary to azathioprine therapy post liver transplantation. However, it is not known whether defibrotide therapy will alter the natural history of the disease once fulminant hepatic failure has developed. The role of prophylactic defibrotide therapy to prevent severe VOD developing has not been defined.

Transjugular intrahepatic porto-systemic shunts (TIPS) have been placed in patients with severe VOD post haematopoietic cell transplantation. However, with no improvement in patient survival recorded, TIPS cannot be recommended as a treatment modality likely to improve clinical outcome.

The role of liver transplantation in the management of severe VOD remains controversial. While liver transplantation has been reported as a treatment option, results have been disappointing. Of the 11 reported cases in the literature, the short to medium term survival is <40%. Interestingly, there have been no case reports describing liver transplantation as a therapeutic option for the management of severe VOD post haematopoietic cell transplantation since 1997. There are several possible reasons for this. It may be related to the introduction of defibrotide therapy into the management armamentarium of treating severe VOD, although there is still a high fatality rate in this group of patients. However, it is reasonably clear from the available evidence that patients failing defibrotide therapy usually have established multi-organ failure, and are unlikely to survive liver transplantation. A further possibility is that the incidence of severe VOD has significantly reduced over recent years, so that liver transplantation is performed so infrequently that it has not been reported. Looking at the experience
from Birmingham, three patients were listed for liver transplantation, of whom only one survived long enough to receive a graft. The one patient who underwent liver transplantation subsequently died of multi-organ failure.

On the basis of the limited data available, it is difficult to recommend the use of a scarce resource such as liver transplantation in this clinical setting. Therefore, in the management of severe fulminant hepatic VOD post haematopoietic cell transplantation complicated by renal and respiratory failure, liver transplantation has no established role. However, for early fulminant liver failure secondary to VOD (not yet complicated by multi-organ failure), where there is a good chance of cure of the underlying malignancy by haematopoietic cell transplantation, liver transplantation should be considered. Clearly these will be highly selected cases. It must also be remembered that in this group of patients, post liver transplant immunosuppression management is fraught with difficulty, because of the increased risk of infective and bleeding episodes related to cytopenias, and the much greater potential for drug interactions.

Liver transplantation may also be a therapeutic option when patients have survived long enough to develop long-term complications of portal hypertension, and have an otherwise good outcome from bone-marrow transplantation. This group of patients will suffer principally from ascites, and should have also failed conventional medical and radiological therapies before being considered for liver transplantation.

Clearly the best way of treating severe VOD following haematopoietic cell transplantation is by prevention. By identifying high-risk factors prior to the initiation of myeloablative therapy, low-risk conditioning regimens may be used. Prophylaxis with UDCA may be helpful in reducing the incidence of severe VOD. Once moderate to severe VOD is established, treatment with defibrotide improves clinical outcome. Fulminant liver failure which develops as a consequence of severe VOD is generally associated with multi-organ failure, and has a dismal prognosis. In this clinical setting, palliative care becomes important, as liver transplantation is most often not indicated and prolongation of life with intensive care may be inappropriate.

Acknowledgements

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