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SHORT COMMUNICATION

Intestinal perforation associated with rituximab therapy for post-transplant lymphoproliferative disorder after liver transplantation

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Abstract Post-transplant lymphoproliferative disorder (PTLD) is a serious complication after organ transplantation with a cumulative incidence of 1.1% at 18 months and 4.7% at 15 years. It has been reported in patients with or without concomitant Epstein–Barr virus infection. Therapy ranges from a reduction of immunosuppression to administration of conventional cytotoxic chemotherapy. Rituximab, a recombinant chimeric anti-CD20 monoclonal antibody has been used for the treatment of PTLD with promising results and a reduction in treatment-associated mortality. However, the use of rituximab has been associated with spontaneous gastrointestinal perforation. We describe a case of recurrent intestinal perforations after a single dose of rituximab.

Keywords Post-transplantation lymphoproliferative disorder · Intestinal perforation · Rituximab · Liver transplantation · Complication

Introduction

Post-transplantation lymphoproliferative disorder (PTLD) is a serious complication after liver transplantation. This occurs more frequently in the first year with a cumulative incidence of 1.1% at 18 months and 4.7% at 15 years [1]. PTLD reflects a wide range of B-cell proliferation and develops as a consequence of pharmacological immunosuppression after transplantation in patients with or without concomitant Epstein–Barr virus (EBV) infection. Rituximab or Rituxan (BIOGEN-IDEC Pharmaceuticals and Genetech Inc., San Francisco, CA), a chimeric monoclonal antibody of the CD20 antigen on the surface of B lymphocytes has been used in the last decade for the treatment of PTLD. Therapy with rituximab has been associated with intestinal perforations due to the rapid chemotherapeutic lysis of tumors in the gastrointestinal tract. This is a rare complication after its administration and reports in the literature are sparse. We present a case of recurrent intestinal perforations after a single dose of rituximab in a patient with late onset EBV-negative PTLD after liver transplantation.

Case report

A 60-year-old male suffering from chronic hepatitis C virus infection and alcoholic cirrhosis underwent an orthotopic liver transplantation in late 2003. His maintenance immunosuppression consisted of low-dose tacrolimus. His course after transplantation was complicated by recurrent hepatitis C infection and intractable ascites. In August 2008, the patient was seen for a 4-month history of diffuse abdominal pain. On physical exam, the patient was noted to have a palpable right inguinal lymph node and an incarcerated umbilical hernia. Thoracic and abdominal computed tomography revealed generalized lymphadenopathy. Therefore, we performed an incisional lymph node biopsy along with an umbilical hernia repair. During the hernia repair, a 3-cm tumor was discovered in the jejunum extending into the

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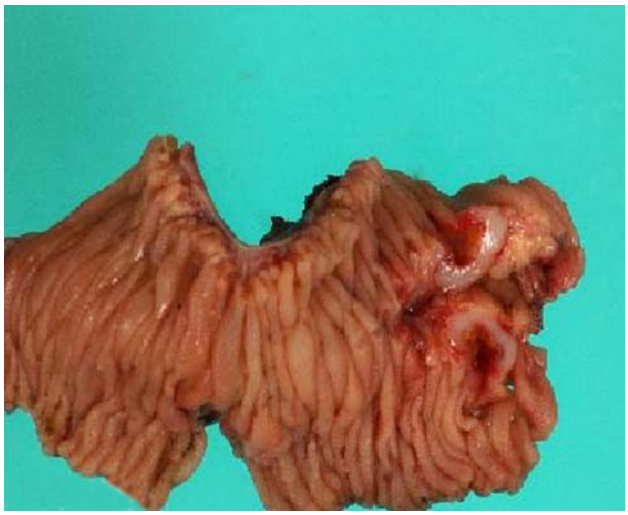

Fig. 1 Jejunal resection specimen containing a 3-cm tumor

mesentery. Consequently, a small bowel resection to include the entire tumor was performed along with excising the inguinal lymph node (Fig. 1). Of note, there were multiple smaller tumors in the small bowel wall and associated mesentery. Pathology analysis of both specimens revealed diffuse large B-cell lymphoma (DLBCL). The cells stained weakly positive for CD20 and BCL-2 and strongly positive for CD10 and BCL-6 (Fig. 2). In situ hybridization for Epstein–Barr virus (EBV) RNA on tissue was negative. This was consistent with EBV-negative B-cell PTLD of DLBCL-type. The tacrolimus dose was decreased from 0.5 mg twice a day to 0.5 mg daily and therapy with rituximab in the standard dosing of 375 mg/m² was given without immediate adverse events [2]. No other chemotherapeutic drug was used. Three days later the patient was discharged from the hospital on low-dose tacrolimus.

Five days after rituximab infusion, the patient returned to the emergency department complaining of generalized abdominal pain with findings of peritonitis on exam. Pneumoperitoneum was present on plain abdominal radiography. Exploratory laparotomy revealed two intestinal perforations in the jejunum. The previous small bowel anastomosis was intact. The patient underwent small bowel resection with primary anastomosis of the mid-jejunum and repair of the other perforation. Histology revealed focal mucosal necrosis with transmural inflammation. The patient's postoperative course was complicated, but he eventually had return of bowel function. Twenty days after the initial rituximab infusion, the patient had an episode of projectile vomiting and generalized abdominal pain. On exam, the patient had peritonitis and significant pneumatosis intestinalis was seen on abdominal computed tomography (Fig. 3). A second laparotomy revealed two new perforations in the distal jejunum which were repaired. Interestingly, gross areas of lymphoma were no longer evident. Unfortunately, the patient clinically declined in the immediate postoperative period from multi-system organ failure and died.

Discussion

There are no large, prospective, randomized trials that would provide clear guidelines for PTLD treatment. The

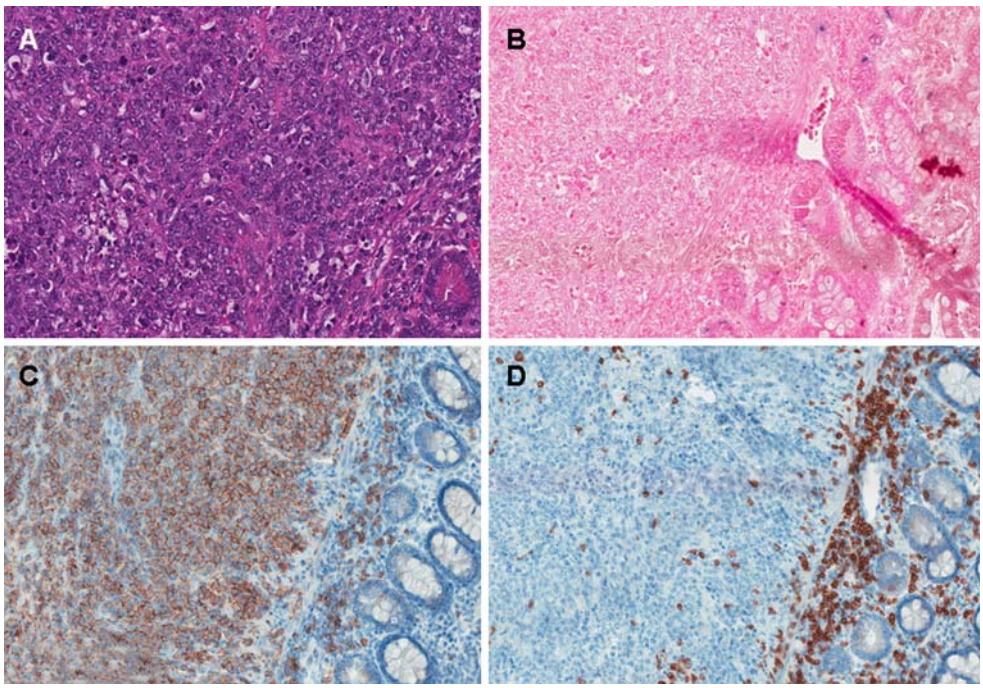

Fig. 2 EBV-negative monomorphic B-cell PTLD of DLBCL-type. Large cells with irregular nuclear contours and prominent nucleoli. The tumor demonstrates high mitotic rate and apoptotic cells (hematoxylin and eosin) (**a**). The EBER in situ hybridization stain for EBV is negative (**b**). The cells stain weakly positive for CD20 (**c**) and negative for CD3 (T-cell marker) (**d**)

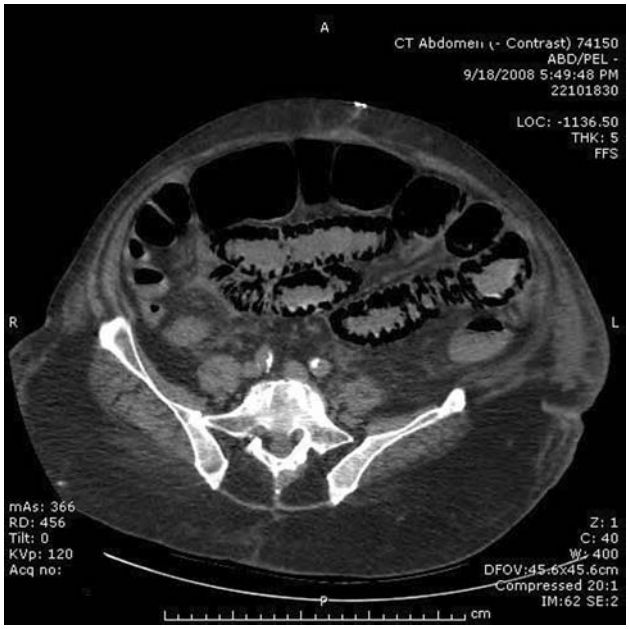

Fig. 3 Pneumatosis intestinalis seen on abdominal CT scan

current conventional therapy for PTLD is reduction or withdrawal of immunosuppression and, in resistant cases or in patients not amenable for reduction in immunosuppression, administration of conventional cytotoxic chemotherapy [2]. In the last decade, rituximab has been used for the treatment of PTLD with promising results and significant reduction in toxicity and treatment-associated mortality when compared with chemotherapy [2]. However, the use of this recombinant chimeric anti-CD20 monoclonal antibody has been associated with spontaneous gastrointestinal perforation [3–5]. In 2006, a warning was sent out by Roche Pharmaceuticals about the risk of intestinal perforation with rituximab. The company identified 37 cases of gastrointestinal perforations based on approximately 730,000 cumulative patient exposures, resulting in 4 fatalities. In addition, a pooled analysis of clinical trials in patients with non-Hodgkin lymphoma revealed a higher frequency of gastrointestinal perforation with rituximab and chemotherapy versus chemotherapy alone (0.38 and 0.15%, respectively) [6, 7]. Rituximab attacks the CD20 receptors causing lysis of the tumor cells. Postulated mechanisms of the tumoricidal activity of rituximab include complement-dependent cytotoxicity, antibody dependent cell-mediated cytotoxicity and induction of apoptosis [8]. The first report of intestinal perforation after rituximab infusion in a patient with PTLD was by Kollmar et al. [4]. He suggested that the aggressive tumor lysis response may be related to the high CD20 expression of PTLD tumors. Nevertheless, in our patient the tumor cells stained weakly positive for CD20 showing that the response to rituximab in relation with the degree of expression of this marker is not an accurate predictor of response.

This complication has been reported especially in elderly patients with gastrointestinal manifestations of PTLD, multiple sites of involvement and advanced disease [3–5]. The prognosis in patients with advanced disease is poor [9], however, in the setting of localized disease the treatment of PTLD may result in involution of gastrointestinal lesions. Therefore, early diagnosis of gastrointestinal PTLD and a high index of suspicion are important. Any gastrointestinal symptomatology should prompt a thorough diagnostic evaluation. In this case the diagnosis was made at a late stage. At the time of his initial gastrointestinal symptomatology, a complete workup with esophagogastroduodenoscopy, colonoscopy, computed tomography and biopsy of any suspicious lesion may have been helpful in making an early diagnosis and therefore decreasing the risk of this catastrophic complication.

Cytotoxic chemotherapy was considered unsafe for this patient due to his age, immunosuppressed state and underlying liver dysfunction. Given the reported low toxicity of rituximab compared with cytotoxic chemotherapy, we used the former as first-line therapy in conjunction with the reduction in immunosuppression.

In this case the donor and the recipient both had quiescent EBV infection at the time of transplantation. In this population, late onset and EBV-negative PTLD are more common [1]. There is data that suggest that late onset or EBV-negative tumors are less likely to respond to rituximab therapy [2]; however, there are also reports where rituximab has been successful in EBV-negative cases with extensive involvement [10]. In this regard, further studies are required to investigate the efficacy of rituximab therapy in this particular population of patients. Unfortunately, the rare incidence of PTLD makes it difficult to perform large prospective trials. In our institution, the incidence of PTLD after liver transplantation is 2% (23 patients out of 1,132 in the last decade). Rituximab had been used alone or in association with other chemotherapeutic drugs without serious side effects up to the present case. Rituximab seems to be a good therapeutic option for PTLD with a low risk of serious side effects. We conclude that Rituximab should be used with caution in patients with gastrointestinal manifestations of PTLD, especially in advanced disease and multiple sites of involvement due to the risk of gastrointestinal perforation. Attention should focus on identifying patients at risk for this complication by performing a careful patient selection before its administration. Most of the perforations occur between 1 and 6 days after administration [7], therefore, therapy with rituximab should be done in a controlled setting and not as an outpatient therapy especially in high-risk patients.

References

1. Kremers WK, Devarbhavi HC, Wiesner RH, Krom RA, Macon WR, Habermann TM (2006) Post-transplant lymphoproliferative disorders following liver transplantation: incidence, risk factors and survival. Am J Transplant 6(5 Pt 1):1017–1024
2. Svoboda J, Kotloff R, Tsai DE (2006) Management of patients with post-transplant lymphoproliferative disorder: the role of rituximab. Transpl Int 19(4):259–269
3. Hsu YC, Liao WC, Wang HP, Yao M, Lin JT (2007) Catastrophic gastrointestinal manifestations of post-transplant lymphoproliferative disorder. Dig Liver Dis 13 December [Epub ahead of print]
4. Kollmar O, Becker S, Schilling MK, Maurer CA (2002) Intestinal lymphoma perforations as a consequence of highly effective anti-CD20 antibody therapy. Transplantation 73(4):669–670
5. (No authors listed) (2002) Rituximab: first report of intestinal perforations in an elderly patient: case report. Reactions. 2002:1(901):14–15(2)
6. (No authors listed) (2007) Rituximab: gastrointestinal perforation. Prescrire Int October;16(91):201
7. Health Canada, reports of bowel obstruction and gastrointestinal perforations with Rituxan. Rituximab. 10 November 2006. Website: http://www.hc-gc.gs.ca. Accessed October 2006, 3 p
8. Ifthikharuddin JJ, Mieles LA, Rosenblatt JD, Ryan CK, Sahasrabudhe DM (2000) CD-20 expression in post-transplant lymphoproliferative disorders: treatment with rituximab. Am J Hematol 65(2):171–173
9. Leblond V, Dhedin N, Mamzer Brunel MF, Choquet S, Hermine O, Porcher R et al (2001) Identification of prognostic factors in 61 patients with posttransplantation lymphoproliferative disorders. J Clin Oncol 19:772–778
10. Tang MB, Tan ES, Tan SH (2008) Late onset Epstein Barr virus negative post-transplant lymphoproliferative disorder presenting as ulcerated necrotic papules and nodules in a renal transplant patient. Australas J Dermatol 49(2):100–102