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Case Report

Surgical Management of Perforated Gastrointestinal Posttransplantation Lymphoproliferative Disorder After Heart Transplantation

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Posttransplantation lymphoproliferative disorder (PTLD) is a relatively rare and life-threatening complication after organ transplantation. From 1999 to 2012, 45 adult patients underwent heart transplantation at our hospital. Two of the patients developed PTLD after transplantation and required emergency surgery due to intestinal perforation. These cases were informative regarding the adequate surgical management of such cases. Both cases revealed Epstein-Barr virus-related PTLD. The optimal treatment of PTLD remains controversial, and PTLD with gastrointestinal perforation could be critical because the patients are already debilitated and immunocompromised after transplantation. Therefore, the nonspecific abdominal symptoms can be diagnostic for PTLD, and proper surgical intervention should be performed immediately. We present these two suggestive and rare cases in regard to the management of perforation with PTLD and a review of literature.

Key words: Lymphoma – Intestinal perforation – Posttransplantation – Lymphoproliferative disorder – Transplantation

Posttransplantation lymphoproliferative disorder (PTLD) is a serious complication after solid organ transplantation. PTLD occurs in up to 10% of transplant recipients, but the incidence varies based on the transplanted organ.[1] PTLD occurs in 1%–6% patients who receive a heart transplant. According to previous reports, PTLD is associated with Epstein-Barr virus (EBV), which leads to uncontrolled B cell proliferation and tumor formation.[2] PTLD occurs in various organs, but involvement of the

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gastrointestinal (GI) tract causes GI perforation.[3] GI perforation can be life-threatening because the patients are already debilitated and immunocompromised after transplantation or receiving chemotherapy for PTLD. However, the optimal management of PTLD with GI perforation is controversial because no firm evidence exists for the optimal treatment of perforated PTLD. Primary anastomosis is typically avoided in GI perforation with general peritonitis.[4] However, recent reports suggest that resection and primary anastomosis can be performed safely in certain surgical conditions and with sophisticated surgical techniques.[5] From 1999 to 2012, 45 adult patients underwent heart transplantation at our hospital. Two of the patients developed PTLD after transplantation and required surgical management due to intestinal perforation. We present these two suggestive and rare cases in regards to the management of perforation with PTLD and a review of literature.

Case 1

A 48-year-old man received a heart transplant due to dilated cardiomyopathy in June 2011. His immunosuppressive medication consisted of 7.5 mg of tacrolimus hydrate twice daily, 1000 mg of mycophenolate mofetil twice daily, and 5 mg of predonine once daily. The level of serum tacrolimus was around 4.4 ng/mL. Eleven months after transplantation, the patient had a persistently high fever and severe anemia. Esophagogastroduodenoscopy revealed multiple ulcers in the stomach and jejunum, and histologic study of a biopsy specimen did not reveal malignancy. Proton pump inhibitor therapy was initiated. In June 2012, the patient suddenly complained of lower abdominal pain. Clinical examination revealed maximum tenderness in the right lower abdomen, and rebound tenderness was observed. Computed tomography (CT) scans showed massive free air and fluid collection around the intestine in the pelvis (Fig. 1). We diagnosed intestinal perforation and performed an emergency operation. At laparotomy, 2 perforations were identified in the ileum 20 cm from the terminal ileum. Little feces were present, and the adjacent intestine seemed to be a suitable condition for primary anastomosis. Therefore, the patient underwent ileocecal resection with primary anastomosis. Histologic examination of a specimen revealed multiple ulcers, perforation, and the invasion of polymorphic lymphoid cells positive for CD3 and CD20. These cells were also EBER-positive (Fig. 2). These findings indicated EBV-positive PTLD.

Regarding the postoperative course, anastomotic leakage occurred 8 days after surgery. We performed surgery again to resect the anastomosis site and to perform an ileostomy and colostomy. During the postoperative course, the patient was managed jointly by a cardiovascular surgeon and a hematologist. Reduction of immunosuppression and administration of rituximab was started. The patient experienced complete remission 5 months after the first surgery.

Case 2

An 18-year-old man underwent heart transplantation due to dilated cardiomyopathy in January 2012. Immunosuppressive therapy consisted of 4 mg of tacrolimus hydrate twice daily, 1000 mg of mycophenolate mofetil twice daily, and 5 mg of predonine once daily. The level of serum tacrolimus was around 10 ng/mL. In June 2012, the patient presented with neck lymphadenopathy, axillary lymphadenopathy, and abdominal pain with 2-week duration. Hematologic examination revealed anemia and an inflammatory reaction. Esophagogastroduodenoscopic examination to investigate the anemia revealed a gastric ulcer and duodenum ulcer. Histologic examination of the biopsies revealed monomorphic lesions diagnosed as diffuse large B-cell lymphoma (DLBCL), and the cells stained positive for CD20. The EBV genome was identified by in situ hybridization for EBV early RNA (EBER; Fig. 3). Pathology analysis of the incisional lymph node biopsy and an axillary lymph node revealed DLBCL with CD20-positive cells. These findings were consistent with EBV-positive B-cell PTLD of the DLBCL type. We reduced the immunosuppressive medication and started rituximab. Three days after rituximab infusion, the patient presented with diffuse abdominal pain and a fever of >39°C. Abdominal CT revealed free air under the abdominal wall (Fig. 4). We suspected intestinal perforation and performed an emergency operation. Laparotomy revealed localized pus-like ascites, and 3-cm and 3.5-cm perforated tumors were identified 0.7 and 0.4 m from the ligament of Treitz, respectively. Consequently, we performed small bowel resection of the area including the 2 perforated tumors and constructed an ileostomy 35 cm from the ligament of Treitz without primary anastomosis. Pathologic analysis of the tumor revealed CD20 and CD3-positive DLBCL (Fig. 3).

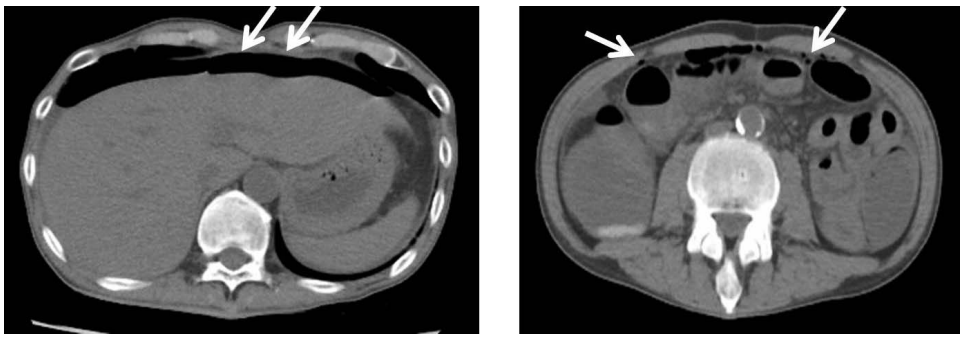

Fig. 1 CT scans of case 1 revealing free air.

This finding is consistent with the histologic examination of the gastric biopsy. In the postoperative course, the patient was managed jointly by a cardiovascular surgeon and a hematologist. His condition was managed by reducing immunosuppression and chemotherapy for DLBCL. The patient experienced complete remission 5 months after surgery and remains well without any signs of relapse.

Discussion

PTLD is a well-recognized, potentially fatal complication after solid organ transplantation and encompasses a broad spectrum of tumors, ranging from benign polyclonal lymphoid proliferation to high-grade malignant lymphoma.[6] One study reported an incidence of 692/100,000 person-years in heart and/or lung transplant recipients.[7] The incidence of PTLD after solid organ transplantation is markedly

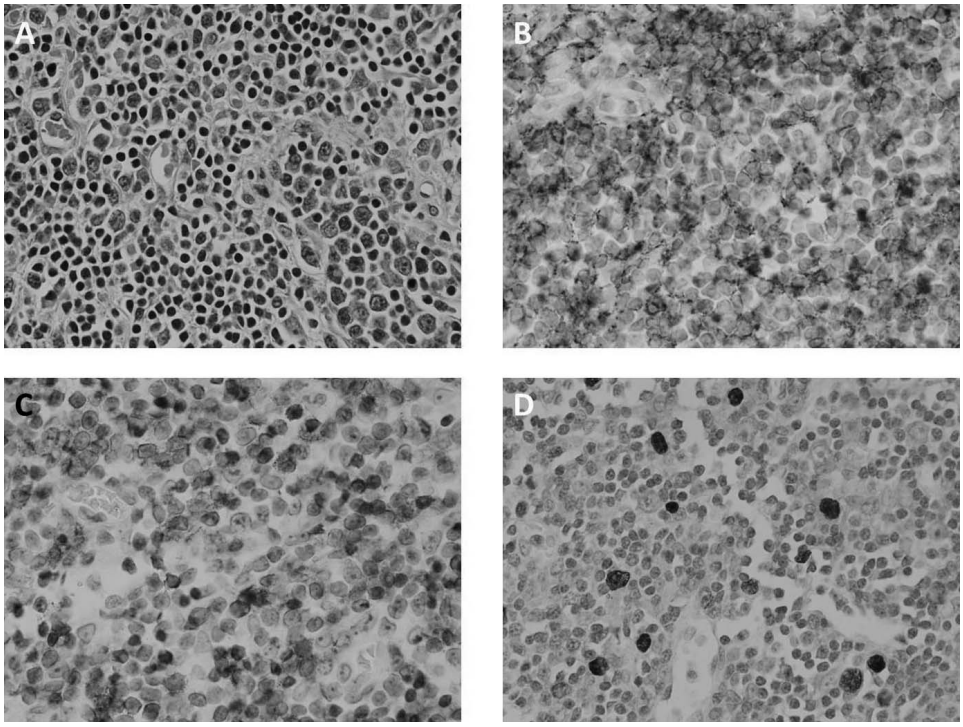

Fig. 2 Histologic examination of case 1. The specimen from the resected ileum exhibited a polymorphic structure with irregular nuclear contours and prominent nucleoli (A). The cells stained positive for CD 20 (B) and CD3 (C). The EBER in situ hybridization stain for EBV was positive (D). These findings are consistent with EBV-positive PTLD.

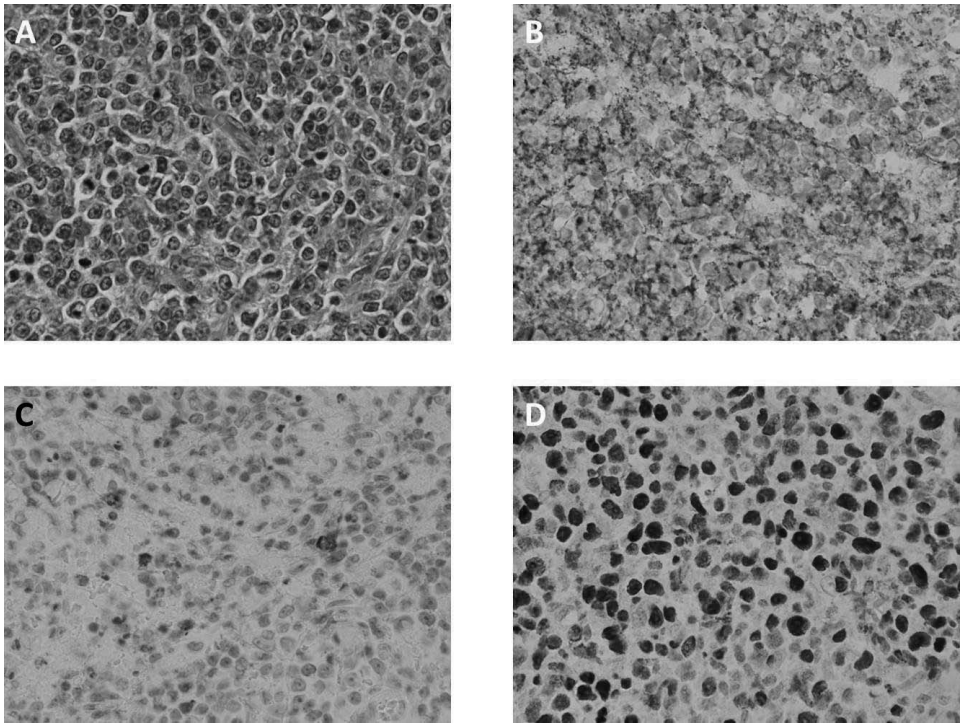

Fig. 3 Histologic examination of case 2. The specimen from the resected ileum exhibited monomorphic large cells with irregular nuclear contours and prominent nucleoli (A). The cells stained positive for CD 20 (B) and weakly positive for CD3 (C). The EBER in situ hybridization stain for EBV was positive in the histology of the gastric biopsy specimen (D). These findings are consistent with EBV-positive B-cell PTLD of the DLBCL type.

different in children and adults, and it varies according to the type of organ transplant. In adult recipients, PTLD has been reported to occur in 1%–2.3% of kidney transplants, 1%–2.8% of liver transplants, 1%–6.3% of heart transplants, 2.4%–5.8% of heart-lung transplants, and 4.2%–10% of lung transplants.[2,8]

Several factors have been implicated to increase the risk of developing PTLD in adult transplant recipients, such as the use of antilymphocyte antibodies, younger age, fewer human leukocyte antigen matches, hepatitis C virus infection, EBV seronegativity at the time of transplantation, and a history of splenectomy.[9–11] Most cases of PTLD after solid organ transplantation are associated with EBV. In immunocompromised subjects, T-cell function is impaired, which may lead to uncontrolled proliferation of EBV-transformed B-cells. The risk of PTLD

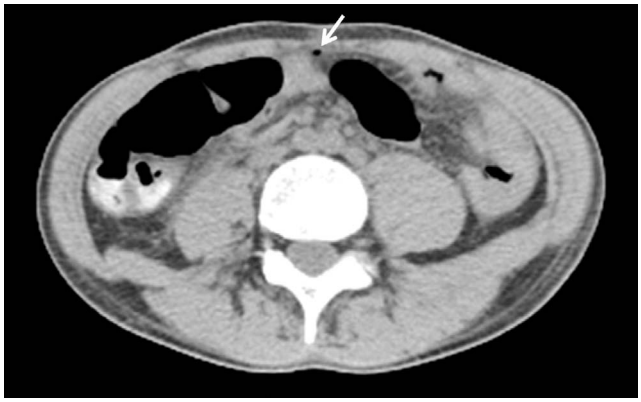

Fig. 4 CT scan of case 2 revealed free air under the abdominal wall.

is increased when an EBV-negative recipient receives a transplant from an EBV-positive donor.[12,13] According to the 2008 World Health Organization (WHO) classification, PTLD is divided into 4 major categories based on morphologic, immunophenotypic, and molecular criteria: 1) early lesion; 2) polymorphic PTLD; 3) monomorphic PTLD; and 4) classical Hodgkin lymphoma.[6] Most PTLDs are of B-cell origin with approximately 5% being T-cell and T/NK cell origin. The majority of B-cell PTLDs are EBV-positive (60%–70%), while most T/NK subtypes (>90%) are EBV-negative.[14] The histologic examination of case 1 revealed EBV-related diffuse large B-cell lymphoma, and the examination of case 2 found EBV-related polymorphic PTLD. Both cases developed PTLD within 1 year. This observation is consistent with previous reports that the risk of EBV-related PTLD after solid organ transplantation is highest within the first year of transplantation.[6,15–18]

The symptoms of PTLD vary depending on location and the degree of organ involvement, including fever, lymphadenopathy, weight loss, anorexia, fatigue, sepsis, and multi-organ dysfunction. Extranodal involvement includes gastrointestinal tract, lung, skin, bone marrow, and central nervous systems.[8,19]

The primary goal in the treatment of PTLD is both curing disease and preserving graft function. However, reduced immune suppression and rituximab-based therapy have shown to play a crucial role in treating this complex disorder. In our 2 cases, we reduced immunosuppression therapy and administered chemotherapy including rituximab, and both patients had complete remission. Some studies have reported that the use of rituximab, a recombinant chimeric anti-CD20 monoclonal antibody, is associated with spontaneous GI perforation.[20,21] Most of the perforations occur between 1 and 6 days after administration.[22] Accordingly, the patient should be observed closely when administering this drug.

Many reports have investigated the optimal surgical procedure for managing generalized peritonitis due to acute perforation of the left colon. Immediate resection of the diseased colonic segment with an end colostomy is generally recommended. In contrast, some reports have favored colonic resection with primary anastomosis.[23] An additional diverting stoma was routinely performed in most of these reports. However, several recent reports indicate that primary anastomosis without diverting ileostomy can be performed safely in certain surgical conditions, including emergency operations.[4,24] These reports are suggestive for our cases, but the optimal surgical management of PTLD patients with GI perforation is unclear because the rate of incidence is very low (0.28%).[3] We also should consider the difference of postoperative management between the patient's undertaken transplantation and the others. The former are immunosuppressive status and we admit them the immunosuppression in the early postoperative stage in order to save the transplanted organ. It may cause the systemic infection to become serious. Furthermore, there are some reports that immunosuppression is one of the risk factors of anastomotic leakage owing to delayed wound healing and ostomy treatment diminished the consequences of risk and reduces the need for emergency re-operation.[25–27]

In case 1, laparotomy showed that the degree of intra-abdominal infection was mild, and the condition of the bowel seemed to be good. We are afraid that construction of an ileostomy would make fluid management more difficult after surgery. Therefore, we performed resection of the perforated bowel and primary anastomosis. However, 8 days after surgery, anastomotic leakage occurred and required additional emergency surgery. Reflecting on the occurrence of anastomotic leakage in the postoperative course of case 1, we resected the perforated jejunum and constructed a jejunostomy in case 2 in order to continue the treatment for PTLD safely with surviving graft function. In this case, the postoperative course was good and we were able to close the stoma 6 months after primary surgery. These 2 cases suggest that a stoma is beneficial in the surgical management of GI perforation with PTLD.

There is a wide range of prognostic factors, because PTLD is heterogeneity disease. However, several common features have been identified as poor prognostic factors, such as increased age, elevated LDH, presence of B symptoms, multi-organ involvement, decreased performance status, advanced stage disease, involvement of the allograft, and >1 extranodal site.[11,28]

In conclusion, we presented 2 cases of PTLD complicated by GI perforation and requiring emergency surgery. With the increasing number of organ transplants and the development of medication for posttransplant management, the incidence of PTLD will increase in the future. PTLD with GI perforation could be critical because the patients are already debilitated and immunocompromised after transplantation. Therefore, we should be highly suspicious of PTLD when the patients who undergo

transplantation have nonspecific abdominal symptoms. The optimal treatment of this disease remains controversial, and further studies are necessary to elucidate the nature of this disease and determine optimal treatment strategies.

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