

Posttransplantation lymphoproliferative disorder involving liver after renal transplantation

Yong Moon Shin

*Department of Radiology and Research Institute of Radiology, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea*

INTRODUCTION

Posttransplantation lymphoproliferative disorder (PTLD) is a serious complication following solid organ transplantation. Most of PTLD is related to an interaction of Epstein-Barr virus (EBV) infection and immune suppression.^{1,2} PTLD occurs most common after intestine transplantation and the least common after renal transplantation.^{3,4} PTLD can involve any organs. Abdominal organs are frequently involved, and up to 50% of all cases of PTLD are confined to the abdomen.⁵ The disease manifestation and the anatomic pattern of organ involvement is highly dependent on the type of transplantation.

To provide more detailed understanding of hepatic involvement of PTLD, here a case of PTLD involving liver after renal transplantation is presented with radiological imaging findings. A review about classification and clinical considerations and the imaging features of PTLD involving liver will be discussed. Familiarity with the imaging findings of this disorder can help early and accurate diagnosis and result in better prognosis.

CASE SUMMARY

A 17-year-old male was admitted with the complaint of generalized abdominal pain. He had history of end stage renal disease due to focal segmental glomerulosclerosis. He got kidney transplantation 6 years ago. Kidney donor

was his mother. He had also history of acute rejection immediately after kidney transplantation, and managed with plasmapheresis and immunosuppression. He was managed with drugs including Tacrolimus (Prograf[®], Astellas, Tokyo, Japan), mycophenolate mofetil (Cellcept[®], Roche, Basel, Switzerland), and Deflazacort (Calcort[®], Sanofi-aventis, Paris, France) for six years with gradual dose reduction.

He complained generalized abdominal pain for three days, and visited hospital. He presented symptoms such as fever and night sweating, but no weight loss, dizziness, dyspnea, anorexia, nausea, vomiting, diarrhea or other abdominal symptoms were presented. He presented physical examination findings including hepatomegaly with three finger width and mild abdominal distension.

The laboratory findings showed hemoglobin 8.5 g/dL, white blood cell count 8,500/mm³, (neutrophil 63.2%, lymphocyte 22.1%), platelet count 284,000/mm³. Biochemical tests showed that the serum level of alanine aminotransferase was 24 IU/L, aspartate aminotransferase was 45 IU/L, and alkaline phosphatase was 99 IU/L. Serum protein was 5.7 g/dL and albumin was 2.9 g/dL. Total bilirubin was 0.5 mg/dL. Blood urea nitrogen (BUN) was 20 mg/dL and creatinine was 1.3 mg/dL. Serum amylase was elevated as 590 U/L, but lipase was 22 U/L. Lactate dehydrogenase was 1,612 IU/L and β -2 Microglobulin was elevated to 6.6 μ g/mL. Alpha-fetoprotein was less than 1 ng/mL. Hepatitis B surface (HBs) antigen and anti-HBs were negative.

Keywords: Liver; Transplantation; Lymphoma; Computed tomography

Abbreviations: CT, computed tomography; EBV, Epstein-Barr virus; FDG-PET, fludeoxyglucose positron emission tomography; PTLD, posttransplantation lymphoproliferative disorder

Corresponding author: Yong Moon Shin

Department of Radiology, Asan Medical Center, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel. +82-2-3010-5946, Fax. +82-2-476-4719, E-mail; cjimage@amc.seoul.kr

Contrast-enhanced abdomen CT was taken. There were multiple, well-defined, homogeneously low attenuated round masses in liver (Fig. 1A and B). Mass size was up to 2.5 cm. Also there were multiple mesenteric mass over 10 cm (Fig. 1C and D). It showed heterogenous enhancement and partial central necrotic low attenuation area. The mesenteric mass showed encasement of mesenteric vessels and thickening of adjacent bowel wall. Ultrasonography showed multiple well-defined homogenous low echoic masses in liver (Fig. 2).

Fludexoyglucose positron emission tomography (FDG-PET)

scan showed multiple hypermetabolic lesions in supra-clavicular area, mediastinal area, liver, mesentery, peritoneum, and multiple bones (Fig. 3).

Percutaneous fine-needle-aspiration biopsy was performed in right lobe mass under ultrasound guidance. Histologic examination of the biopsy specimen showed post transplantation lymphoproliferative disease, monomorphic type (diffuse large B cell lymphoma). Special staining results were as follows: CD20 (+), CD10 (+), bcl-6 (+), CD3 (-), CD5 (-), CD56 (-), CD1a (-), TdT (-), EBV (-). Ki-67 labeling index was 60%.

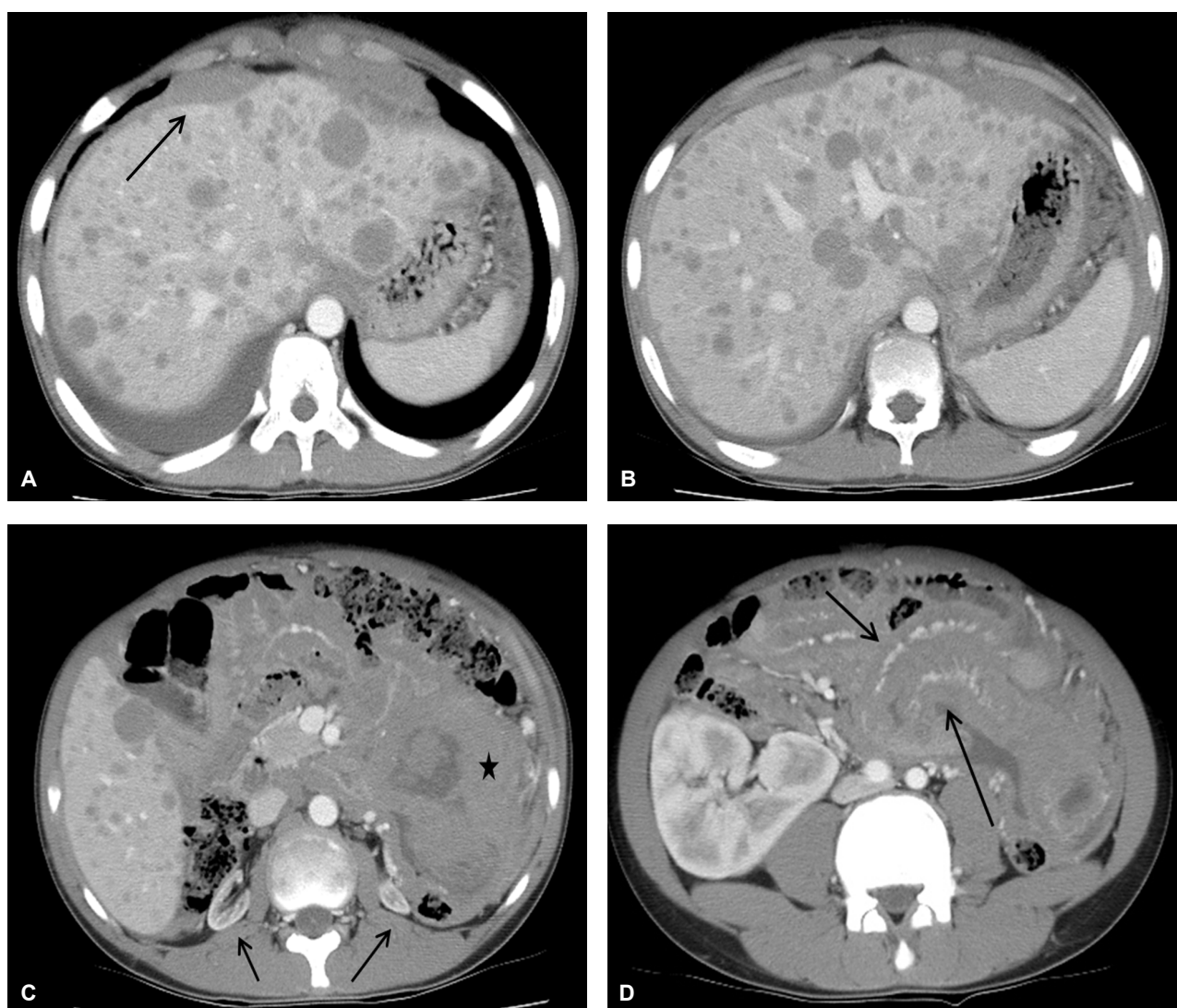


Figure 1. Initial contrast-enhanced abdominal CT scan of a 17-year old male. (A) There were multiple low attenuated mass in liver. There were also homogenous attenuated tumor mass in right cardiophrenic area (arrow) and right pleural effusion. (B) CT scan of another level showed also multiple hepatic mass. (C) CT scan below showed large mesenteric mass (asterisk) with central heterogenous low attenuated area filling in peritoneal cavity. Native kidneys were atrophic due to end stage renal disease (arrows). (D) CT scan in pelvis level showed transplanted kidney in right side. Diffuse infiltrative mesenteric mass with homogenous attenuation encased mesenteric vessels (arrows).

After pathological diagnosis was confirmed, administration of mycophenolate mofetil discontinued and, R-CHOP chemotherapy started. After three months with chemotherapy of four cycles, follow up CT scan was taken. CT scan showed markedly decreased mass in liver and mesentery (Fig. 4A-C). He is alive until now without recurrence after 30 months follow up.

DISCUSSION

PTLD is known as a serious complication of solid organ transplantation following with immunosuppression. Development of lymphoma after transplantation was first described by Doak et al⁶ in a renal transplant recipient in 1968, whereas the term post-transplant lymphoproliferative disorder or disease was introduced by Starzl et al in 1984.⁷

An important risk factor for PTLD development is the

intensity and the amount of immunosuppression administered to the patient.¹ Another risk factor is EBV-seronegative patients receiving allografts from EBV-seropositive donors, consequently leading to primary EBV infection. This is also the main reason for the higher incidences of PTLD observed in pediatric transplant recipients.¹ PTLD are related to infection from EBV, but the presence of this virus is not essential for the diagnosis. EBV-negative PTLD is also



Figure 2. Ultrasonography showed multiple homogeneously low echoic mass in liver.



Figure 3. FDG-PET scan showed multiple hypermetabolic areas in chest, abdomen and bones.



Figure 4. CT scan taken at three months later after systemic chemotherapy. (A) Most of hepatic mass disappeared. (B) CT scan at the same level with Fig. 1C showed that most of mesenteric mass also disappeared. There is small residual shrunken mass around mesenteric root (arrow). (C) CT scan at the same level with Fig. 1D also showed that there is no residual mass around mesenteric vessels.

recognized as in this case presented above. This type of PTLD tends to develop much later after transplantation and has a significantly worse outcome when compared with EBV-positive PTLD.^{1,2}

Society of Hematology and the World Health Organization generated the current classification system, which identifies four major categories: 1) hyperplastic (or early) lesions; 2) polymorphic (generally monoclonal) lesions; 3) monomorphic (ie, lymphomatous invariably monoclonal) lesions, which are further subcategorized along recognized lines of B-cell, T-cell, or natural killer cell neoplasia; and 4) other lymphoproliferative disorders, including Hodgkin lymphoma.⁸

Most cases develop PTLD within 1 year after the transplantation, although some cases develop several years later. PTLD occurs in up to 5% of transplantation recipient patients, depending on the type of organ transplanted and the type and duration of immunosuppressive treatment.⁵ Allograft involvement by PTLD was more frequent in lung and liver transplant recipients than in kidney and heart transplantation.³ The incidence varies with allograft type, with reported frequencies following transplant of intestines up to 20%, heart 2-10%, lung 4-8% liver 2-8% and kidneys 1%.⁴ However, as many thousands of renal transplants are performed each year, the majority of PTLD are observed in kidney transplant recipients.¹ The abdominal cavity is frequently involved by PTLD, with abdominal disease being seen in 50-75% of patients with PTLD.^{3,9} Extranodal involvement (80% of cases) is more common than nodal involvement (20%) in intraabdominal disease.³ Liver is the most frequently involved abdominal solid organ, with involvement seen in 30-45% of post-liver transplantation PTLD, 40% of post-pancreas transplantation PTLD, 23% of post-heart transplantation PTLD and 10% of post-lung transplantation PTLD.⁹ In another large collaborative study, liver involvement was seen in 22%, 9%, 5%, and 5% of cases of monomorphic PTLD (non-Hodgkin lymphoma) following liver, heart, lung or lung-heart, and kidney transplantation, respectively.¹⁰

Imaging findings of PTLD have much in common with those of lymphoma. Especially imaging features of PTLD have much in common with those of lymphoma related to acquired immunodeficiency syndrome (AIDS), in that extranodal involvement was seen in more than 80% of AIDS-related lymphoma, similar to the frequency of extranodal disease among PTLD patients.^{3,9} However, CT

manifestation of non-Hodgkin lymphoma in general population and PTLD in transplant recipients have important difference that extranodal disease occurs only 25% of non-Hodgkin lymphoma.^{3,5}

CT findings of hepatic involvement of PTLD includes (in descending order of frequency of occurrence) 1) discrete low-attenuation nodular lesions, ranging from 1 to 4 cm, which has reduced enhancement compared with the normal liver parenchyma in the portal venous phase (Fig. 1A and B), 2) ill-defined infiltrative or geographic pattern, which has poorly-marginated but can be identified against a normally enhancing background liver and can resemble focal fatty infiltration, 3) a heterogeneous mass at porta hepatis, which can directly extend into the biliary tree or gallbladder, with resultant hepatomegaly or biliary obstruction.^{3,9,11} On ultrasonography, these hepatic lesions appear hypoechoic (Fig. 2) and they can be confused with liver abscesses on ultrasound.^{11,12}

PTLD can involve other abdominal organs. Splenic involvement is less common, manifesting as focal masses with or without splenomegaly.^{11,12} Imaging findings of hollow viscus involvement also resemble those of lymphoma, although ulceration and perforation is more common in PTLD.^{11,13} It presents with localized circumferential wall thickening, aneurismal dilatation of involved loops, luminal excavation or ulceration, eccentric polypoid mass, extramural extension and intussusceptions.³ Extranodal involvement of peritoneum and abdominal wall can produce diffuse soft-tissue infiltration or discrete lobulated mass.³ The case presented above showed discrete multiple liver mass and both types of peritoneal involvement (Fig. 1A-D). PTLD can affect both native and transplanted kidneys and may manifest as focal renal masses or diffuse infiltration.^{3,5}

In the cases of thoracic involvement, the most frequent imaging finding is nodules with a peripheral and basal predominance. And other findings include air space consolidation, mediastinal lymphadenopathy, pleural or chest wall masses, pericardial or pleural effusions.⁵ Intracerebral PTLD is usually isolated and has similar imaging features to AIDS-related cerebral lymphoma.^{5,14} The characteristic finding is of a cerebral nodule demonstrating hemorrhage, necrosis and peripheral enhancement. Lesions are most commonly seen in the periventricular and subcortical white matter. Biopsy may be required to distinguish between PTLD and other disorders such as atypical infection.⁵

FDG-PET scanning proved superior efficacy compared with conventional CT scanning for staging as well as treatment evaluation.¹ PET scan can be an effective imaging method for early detection and diagnosis of PTLTD.

Treatment of PTLTD always consists of reduction of immunosuppression. In addition, monoclonal antibody therapy and antiviral therapies are frequently applied, and systemic chemotherapy is applied in the case of non-response group. Distinguishing between the polymorphic and monomorphic subtypes is important for treatment planning because the former will often respond to immunomodulation alone, however this distinction is not reliably made on the basis of imaging studies, tissue acquisition is necessary. Tissue confirmation is also required to differentiate between PTLTD and rejection.

SUMMARY

PTLTD is a serious and still frequently observed complication of solid organ transplantation. Liver is frequently involved organ, and well-defined multiple mass are most frequently seen.

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