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Case Report

CASE REPORT

Post-transplant lymphoproliferative disorder of the bladder in a lung transplant recipient

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Abstract

Post-transplant lymphoproliferative disorder (PTLD) occurs in ~5% of solid organ and hematopoietic stem cell transplant recipients. We report a unique presentation of PTLD in the bladder of a lung transplant recipient. Our patient was a 62-year-old female who received a bilateral lung transplant for chronic obstructive pulmonary disease. She presented with fever, left-sided flank pain and foul-smelling urine consistent with urosepsis. An abdominal and pelvic computerized tomography revealed an irregular and nodular bladder wall thickening suspicious for urothelial neoplasm. Cystoscopy revealed multiple bladder masses and biopsy demonstrated non-Hodgkin lymphoma consistent with PTLD. She was treated with a reduction in immunosuppression followed by chemotherapy and achieved remission. PTLD in the lung transplant recipients has been described in the gut, respiratory tract, skin, liver and kidney but not in the bladder. This case highlights the need for maintaining a high clinical vigilance even when transplant recipients present with seemingly benign clinical complaints.

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a known complication following solid organ and hematopoietic stem cell transplantation. The incidence is estimated between 2.5 and 8% in lung transplant recipients [1]. The gastrointestinal and respiratory tracts have been reported as common anatomical locations for PTLD in lung transplant recipients [1]. The mainstay of PTLD management remains reduction in immunosuppression while counterbalancing the risk of rejection. Rituximab has been successfully used in CD-20 positive PTLD [1–3]. The ideal chemotherapeutic regimen for PTLD in lung transplant recipients is unclear [1, 3].

Bladder PTLD has not been previously described in lung transplant recipients. Here, we describe this rare presentation of bladder PTLD with seemingly benign symptoms. We also highlight the key features of PTLD in lung transplant recipients.

CASE REPORT

A 62-year-old female who was cytomegalovirus (CMV) negative and Ebstein–Barr virus (EBV) positive who received a bilateral lung transplant for severe chronic obstructive pulmonary disease (FEV1 15%) with an uncomplicated course for 5 years post-transplantation. She presented with a 24 h history of fever, left-sided flank pain and foul-smelling urine. The patient also had a history of hypertension. She had a 70-pack year history of smoking cigarettes prior to transplantation. Immunosuppressive medications at presentation included prednisone, tacrolimus and prophylactic antimicrobial therapy included bactrim, valganciclovir and itraconazole. Mycophenolate mofetil was discontinued due to persistent leukopenia. Valganciclovir was continued due to CMV viremia. Her physical examination was unrevealing. At presentation, her labs were notable for a leukocytosis (20 000 per microliter with a high neutrophilic count of 18 150 per microliter)

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and mild hyponatremia (122 milliequivalents per liter). Urinalysis was positive for white blood cells, leukocyte esterase and nitrites. Her clinical picture was suggestive of urosepsis. She was started on vancomycin and piperacillin/tazobactam. Urine and blood cultures grew *Escherichia coli* within 48 h of incubation. Her antimicrobial regimen was then de-escalated to ceftriaxone based on culture sensitivities. Computed tomography (CT) of the abdomen and pelvis revealed a non-obstructing nephrolithiasis on the right and irregular, nodular thickening of the bladder wall that was suspicious for a neoplasm (Fig. 1A). Our differential diagnosis included urothelial malignancy, followed by less common non-urothelial malignancy (e.g. squamous cell carcinoma, adenocarcinoma and small cell carcinoma), and non-epithelial tumors (e.g. lymphoma, sarcoma) with a superimposed bacterial infection.

A cystoscopy confirmed multiple bladder masses. Biopsies revealed a non-epithelial malignancy with diffuse monomorphic cells. The histopathology was negative for EBV, positive for lymphoma markers CD-10, B-cell lymphoma 6 protein (BCL-6) and multiple myeloma oncogene 1 (MUM1); and positive for CD-20 (indicative of B-cell origin), oncogene c-MYC (40%) and had a high expression of cell proliferation marker Ki-67 (Fig. 2). These histopathology findings in conjunction with the patient's history of lung transplantation supported the diagnosis of diffuse large B-cell lymphoma consistent with PTLD.

Peri-transplant tests were notable for both the donor and recipient being positive for EBV. The patient was treated with ganciclovir/valganciclovir following transplantation and maintained an undetectable serum EBV level until this presentation. EBV-encoded RNA (EBER) *in situ* hybridization was found to be negative on bladder biopsy tissue samples, but serum levels were now detectable (1009 IU/ml).

After confirming the diagnosis of PTLD, a whole-body positron emission tomography (PET) scan was performed, which revealed an FDG-avid pre-vascular anterior mediastinal lymph node consistent with Stage IV PTLD (Fig. 1B). Our management strategy was 2-fold: a safe reduction in the immunosuppressive therapy to treat PTLD while preventing transplant rejection, followed by chemotherapy with an intention to cure. We decreased her tacrolimus to target serum levels between 4–6 ng/ml instead of 6–8 ng/ml, and she was treated with six cycles of rituximab-cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone (R-CHOP). Post-treatment imaging revealed a reduction in bladder wall thickness (Fig. 3), and resolution of bladder masses were confirmed on cystoscopy. Post-treatment PET scans revealed resolution of all FDG-avid lesions (Fig. 4).

DISCUSSION

Here, we present a unique case of PTLD masquerading as a primary bladder cancer in a lung transplant recipient. Our patient did not have any prior symptoms of urgency, urinary incontinence or any constitutional symptoms suggestive of malignancy prior to presentation. She was asymptomatic from bladder PTLD until she developed *E. coli* urosepsis. Her diagnosis was established due to a thorough work-up which included imaging, cystoscopy, biopsy and a PET scan for staging. Our top differential did not include PTLD. Surprisingly, biopsy of the bladder masses revealed PTLD. Our case highlights the need for maintaining a high clinical vigilance when managing transplant patients, even when they present with seemingly benign complaints.

PTLD is a well-known complication seen in patients who have undergone solid organ or hematopoietic stem cell transplantation. 'Early' PTLD occurs within 1 year of transplantation and 'late' occurs beyond the first year [1, 4]. Approximately, 5% of lung transplant patients remain at risk of developing PTLD [1, 5]. Intrathoracic PTLD occurs most frequently in lung transplant recipients with early disease, whereas extra-thoracic disease tends to occur later (the gastrointestinal tract being the most common site) [2]. However, bladder PTLD has not been previously described in lung transplant recipients.

PTLD is a consequence of abnormal B-cell proliferation; and based on B-cell clonal morphology is categorized as monomorphic or polymorphic. The abnormal B-cell proliferative response is classically seen in conjunction with EBV infection, ranging from benign infectious mononucleosis-like illness and polyclonal hyperplasia to aggressive malignant lymphomas. Although, EBV is thought to be central to the pathogenesis of PTLD, PTLD cases associated with EBV have decreased while EBV-negative PTLD cases have proportionally increased over time from 10 (1990–1995) to 48% (2008–2013) [3, 6]. EBV status does not affect treatment responsiveness and does not impact survival post-treatment [6]. In our case, although both the donor and recipient were EBV-positive, her pathology was negative for EBER *in situ* hybridization supporting a diagnosis of EBV-negative PTLD.

Currently, there are no clinical trials that assess the treatment of PTLD exclusively in post-lung transplant recipients. Both EBV-positive and EBV-negative PTLD respond to a reduction in immunosuppression, which remains first-line therapy [6]. Observational cohorts and Phase II studies support the use of R-CHOP [3] and rituximab monotherapy has been shown to cause remission in CD-20 positive B-cell PTLD [7–11].

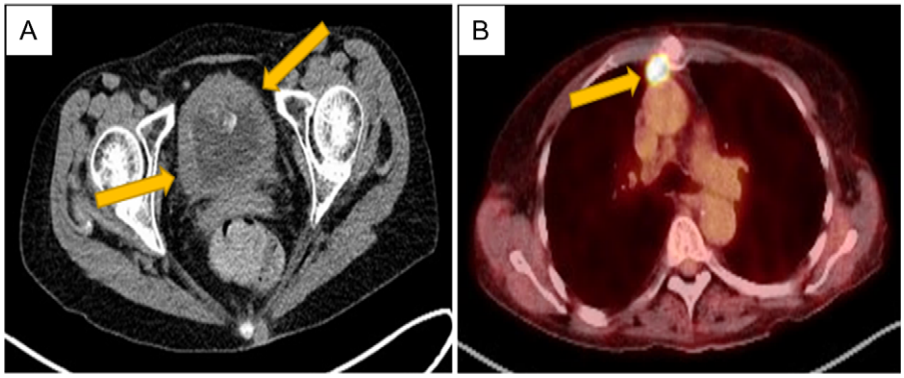

Figure 1: This figure shows the pre-treatment imaging (**A**) CT scan of the abdomen and pelvis with bladder wall thickening (yellow arrows) and (**B**) PET scan with pre-vascular avid lymph node (SUV:14) for staging pre-treatment (yellow arrow).

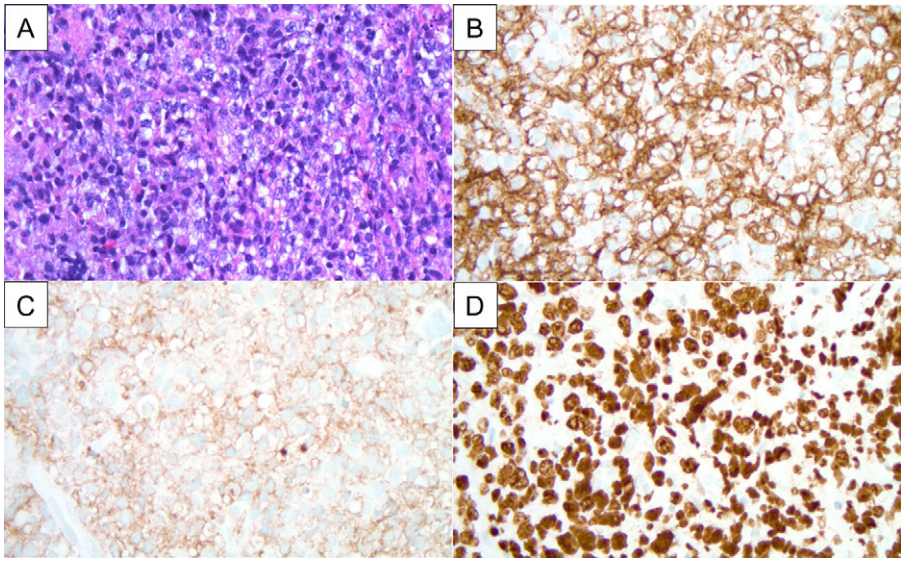

Figure 2: The H&E (**A**) section showed a diffuse sheet of monomorphic large B-cells expressing CD-20 (**B**) and CD-10 (**C**) with a high Ki-67 (D) proliferation fraction (>90%)

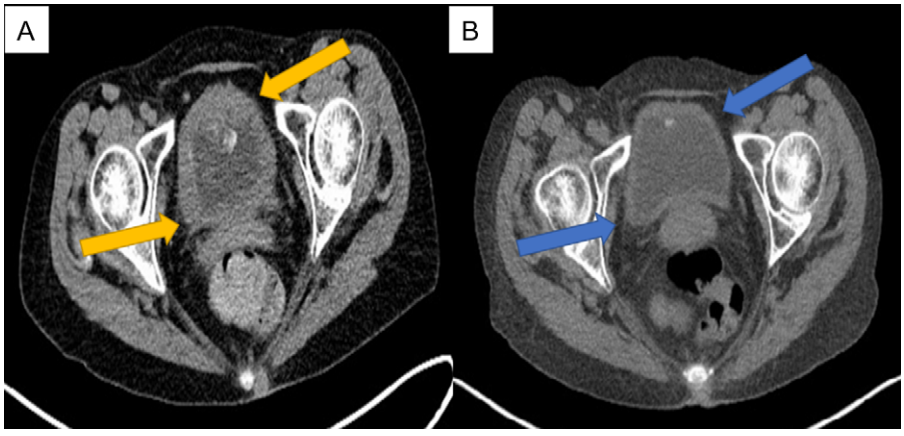

Figure 3: CT scan of the abdomen and pelvis pre-treatment image with yellow arrows (**A**) and post-treatment image with blue arrows (**B**) showing the resolution of the bladder wall thickening.

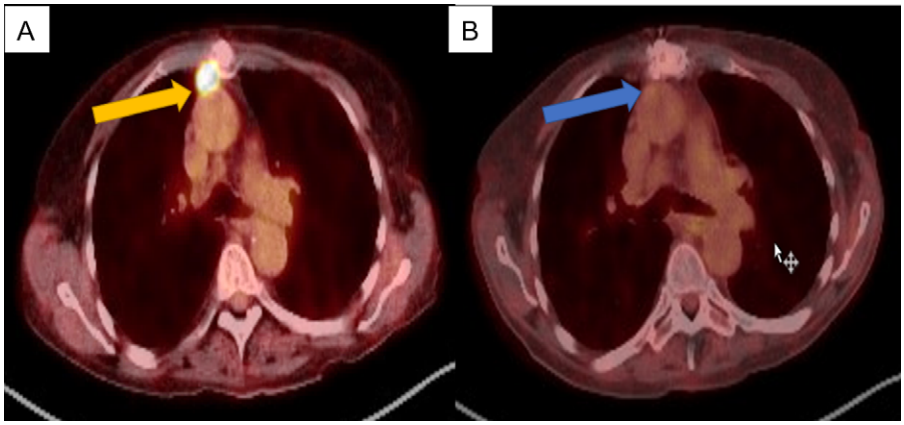

Figure 4: PET scan image of the anterior chest pre-vascular lymph node pre-treatment with yellow arrow (**A**) and post-treatment image with blue arrow (**B**) showing resolution of the PET avid lymph node.

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CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

Not required.

CONSENT

Written consent was obtained from the patient.

GUARANTOR

Drs Harpreet Singh Grewal MD and Atul C. Mehta.

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