Anaplastic large cell lymphoma (monomorphic post-transplant lymphoproliferative disorder) presenting in gallbladder

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Received: 2 August 2010 / Accepted: 10 November 2010 / Published online: 24 November 2010
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Abstract Primary lymphomas of the gallbladder are rare, particularly in the post-transplant setting. Post-transplant lymphoproliferative disorder (PTLD) is a well-described complication of the immunosuppressive therapy employed post-transplant and manifests as a broad spectrum of disease ranging from polymorphic lymphoid proliferations to monomorphic lymphomas. The majority of PTLD consists of B-cell proliferations, although a small subset involves T-cell neoplasms. Of T-cell PTLD, anaplastic large cell lymphoma (ALCL) is a rare subtype. Of note, there are no reported cases of ALCL localized to the gallbladder in either the post-transplant setting or otherwise. We report a case of ALCL (monomorphic PTLD) in a 45-year-old male lung transplant recipient. Within the first year post-transplant, the patient presented with sepsis and acalculous cholecystitis. The patient ultimately underwent an open cholecystectomy and was subsequently found to have ALCL of the gallbladder. Despite aggressive treatment of septic shock, renal failure, and coagulopathy, the patient died 5 days after presentation.

Keywords Post-transplant lymphoproliferative disorder · Gallbladder · Anaplastic large cell lymphoma · Lung transplant

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is an abnormal proliferation of lymphoid cells with a spectrum

ranging from early polyclonal lesions to monomorphic lymphomas indistinguishable from those seen in immunocompetent patients. The lymphoproliferative disorder is believed to develop as a consequence of the immunosuppressive regimens and immune dysregulation present in the transplant setting. Of all the risk factors involved in PTLD, Epstein–Barr virus (EBV) seronegativity at the time of transplant is the most important. Other risk factors include intensity of immunosuppression, which relates to the type of allograft transplanted. Lung transplant recipients have a particularly high incidence of PTLD (reported range of 1.3%–20%) [1]. PTLD is the most common malignancy encountered in lung transplant patients within the first 2 years after transplantation.

Primary lymphomas of the gallbladder are rare. The most common subtypes include diffuse large B-cell lymphoma, marginal zone lymphoma of mucosa-associated lymphoid tissue, follicular lymphoma, and lymphoblastic lymphoma [2]. Rarely, lymphoma may be isolated to the gallbladder with approximately 50 cases reported in the literature [2–5]. In the case of PTLD, the gallbladder can be the primary site or involved secondarily by a systemic lymphoma. Currently, there are no reported cases of anaplastic large cell lymphoma (ALCL) of the gallbladder. We report a case of ALCL of the gallbladder in a lung transplant recipient within the first year after transplantation.

Case report

The patient was a 45-year-old Caucasian man with a past medical history significant for bilateral lung transplantation for chronic bronchiectasis in December 2008. The patient also had a history of celiac disease, diagnosed in spring of 2007, with resolution of symptoms following 2 years on a

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gluten-free diet. He had no risk factors for HIV infection, although his HIV status was unknown. His immunosuppressive medications consisted of tacrolimus, azathioprine, and prednisone. His post-transplant course was complicated by multi-drug resistant *Pseudomonas* and *Stenotrophomonas* infections. Following an extensive sinus surgery for *pseudomonas* infection in late May 2009, the patient developed fevers, dyspnea, and productive cough and presented to the emergency department. He developed sepsis and respiratory failure and was transferred to the intensive care unit (ICU) and intubated. An abdominal ultrasound showed diffuse gallbladder wall thickening, concerning for acalculous cholecystitis. Abdominal CT scan showed a thickened gallbladder and no other definitive findings. His co-morbid conditions included *Clostridium difficile* infection, hypotension, and renal failure. A cholecystostomy tube was placed with no subsequent improvement. The patient became increasingly acidotic. An open cholecystectomy was performed. Post-operatively, aggressive care continued in the ICU, including broad-spectrum antibiotics, continuous venovenous hemodialysis for renal failure, and respiratory support. A left subclavian deep venous thrombosis was found, and the patient was started on heparin. Subsequently, the patient developed bleeding from the nares and mouth, resulting in massive blood loss requiring red cell transfusions. The family of the patient elected comfort care measures. The patient died 5 days after presentation. No postmortem examination was performed.

Pathologic findings

The gallbladder measured $7.2 \times 3.3 \times 1.5$ cm with a wall thickness of 0.9 cm. The gallbladder was edematous. The mucosa had a homogeneous tan color without focal lesions. No calculi were present.

Microscopic examination showed a transmural cellular infiltrate primarily involving the lamina propria and muscularis propria (Fig. 1a). The infiltrate was composed of sheets of intermediate to large cells with high nuclear to cytoplasmic ratios, generous basophilic cytoplasm and prominent nucleoli. Large cells with kidney-shaped nuclei, consistent with hallmark cells, were present (Fig. 1b). Multiple apoptotic bodies and mitotic figures were scattered throughout the infiltrate. Tumor was also found in vessels within the omental adipose tissue suggestive of widespread disease in addition to the disease within the gallbladder.

Immunohistochemical stains were performed. The neoplastic cells expressed CD3, CD7, CD30, and CD45 (Fig. 2a and b). CD4 marked a subset. Ki-67 showed a high proliferative fraction. CD2, CD5, CD8, CD56, CD20, HHV8, ALK-1, and EBER (in-situ hybridization for EBV) were negative (Fig. 2c).

Fig. 1 ALCL involving gallbladder. **a** Transmural infiltrate primarily involving the lamina propria and muscularis propria (hematoxylin and eosin stain, $\times 200$). **b** Sheets of intermediate to large cells with large amounts of basophilic cytoplasm and pleomorphic nuclei including kidney-shaped forms (hematoxylin and eosin stain, $\times 400$)

Based on the histology and immunohistochemistry, anaplastic large cell lymphoma, ALK-negative (monomorphic post-transplant lymphoproliferative disorder) was diagnosed.

Discussion

PTLD occurs in approximately 15% of solid organ transplant recipients. Specifically in lung transplant recipients, the usual site of involvement is the thorax (69%–89% cases), typically involving the allograft. The abdomen is involved in 20%–34% of cases, and mucosal sites (gastrointestinal (GI) tract, airway) and skin may be affected [1]. PTLD may very rarely be isolated to the gallbladder as demonstrated in a case report about a lung transplant recipient who developed EBV-positive polymorphic B-cell PTLD 1 year after transplant [6]. Another more recently described case of PTLD isolated to the gallbladder was reported in a 5-year-old boy, post-cardiac

Fig. 2 Immunohistochemistry. **a** CD7 immunostain marks the neoplastic cells (CD7, $\times 200$). **b** CD30 immunostain highlights the cell membrane and Golgi region of the neoplastic cells (CD30, $\times 200$). **c** ALK immunostain is negative (ALK-1, $\times 200$)

transplant, who developed an EBV-negative PTLD [2]. As with other types of transplantation, B-cell PTLD is much more common than T-cell PTLD (76%–95% vs. 14%, respectively). As discussed previously, risk factors for PTLD

include EBV seronegativity at the time of transplant, age (pediatric patients more susceptible than adults), and possibly, the type of immunosuppressive agents (calcineurin inhibitors, azathioprine, OKT3) [7, 8].

The majority of PTLD arise from B-cells in association with EBV infection. When EBV is reactivated in latently infected cells, several viral proteins are expressed. In an immunocompetent host, the cytotoxic T lymphocytes (CTLs) recognize the viral proteins and kill the virally infected cells. In a transplant recipient, immunosuppression decreases the EBV-specific CTLs, leading to an uncontrolled EBV-induced B-cell proliferation [9]. This process is what is thought to occur in B-cell type PTLD. T-cell PTLD is rare and comprises about 2%–14% of PTLD cases [10]. Most cases of T-cell PTLD present later in the post-transplant course (average 91.8 months), are usually extranodal, and are less responsive to conventional chemotherapy [10]. Approximately 84% are EBV-negative. The etiology of EBV-negative T-cell PTLD is unclear. Possibilities include chronic antigenic stimulation, an unknown viral agent, or T-cells from the transplant itself [11].

Of T-cell PTLD cases, ALCL has rarely been reported [12]. ALCL is a subtype of peripheral T-cell lymphoma and displays a spectrum of disease ranging from primary cutaneous to systemic ALCL. Systemic ALCL is further defined by the presence or absence of anaplastic lymphoma kinase-1 (ALK-1) protein expression. ALK-positive and ALK-negative ALCL are morphologically indistinguishable from one another. The differential diagnosis based on morphology includes peripheral T-cell lymphoma, classical Hodgkin lymphoma, and enteropathy-associated T-cell lymphoma (EATL) [11]. Interestingly, the patient reported here has a history of celiac disease, prompting a consideration of EATL, specifically the anaplastic variant; however, the patient was on a gluten-free diet, and the gallbladder would be a highly unusual site for EATL. In addition, the expression of CD4 and lack of CD56 favor ALCL in this case.

ALCL displays a broad morphologic spectrum, but the mainstay is the presence of hallmark cells (cells with eccentric, horseshoe- or kidney-shaped nuclei). Diagnosis requires uniform expression of CD30 on the large cells. The majority of cases of ALCL are positive for one or more T-cell antigens. When the t(2;5)/NPM-ALK translocation is present, cases will show cytoplasmic and nuclear staining for the ALK protein. ALCL is negative for EBV (EBER and LMP1) [13].

ALCL, ALK-negative, may occur in nodal and extranodal sites, including bone, soft tissue, and skin. The GI tract may also be involved, although the gallbladder has not been a previously reported primary site for ALCL. ALCL, ALK-negative, does not share the favorable prognosis of ALCL, ALK-positive. The overall

5-year survival rate in ALCL, ALK-negative, is 49% as opposed to 70% in ALCL, ALK-positive [14]. Treatment of ALCL in this transplant/PTLD setting generally includes modulation of the immunosuppressive regimen and multiagent chemotherapy.

In conclusion, primary lymphomas of the gallbladder are very rare, particularly in the post-transplant setting. Prior to this case study, there have been no documented cases in the literature of ALCL of the gallbladder, neither in the immunocompetent host nor in the setting of PTLD. Here, we report a case of a lung transplant recipient who developed ALCL of the gallbladder within the first year after transplantation with a fulminant clinical course.

Conflict of interest The authors declare that they have no conflict of interest.

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