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Fatal Case of EBV-negative Posttransplant Lymphoproliferative Disorder With Hemophagocytic Lymphohistiocytosis in an Adult Kidney Transplant Recipient

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Renal transplantation usually requires the administration of lifelong immunosuppressive therapy to minimize rejection.[1] However, while these immunosuppressants are vital to graft protection, they increase the risk of infection and malignancy. Posttransplant lymphoproliferative disorder (PTLD), a troublesome combination of both, covers a wide range of lymphomas, most commonly B-cell type and has been described in pediatric and adult patients.[2] Risk factors for PTLD include Epstein-Barr virus (EBV) infection and immunosuppression and the prevalence of adult kidney transplant PTLD is estimated to be 0.5% to 4%, with the highest incidences occurring within the first year of transplant.[2-5] Although most cases are associated with EBV, EBV-negative PTLD has been described in the literature and is associated with worse outcomes.[4]

Hemophagocytic lymphohistiocytosis (HLH) is a sepsis-like inflammatory syndrome consisting of a hyperferritinemic immune response that can rapidly progress to multisystem organ failure (MOF).[6] There are 2 types of HLH described: primary—associated with different genetic mutations—and secondary, which is more common and associated with infections and malignancies such as EBV and lymphomas.[7] However, very few cases have been described associated with PTLD.[6,8-12] Because HLH can present similarly to sepsis with MOF, it can be challenging for clinicians to discern and treat this condition, especially in transplant recipients.[6] Here, we describe a challenging case of an adult kidney transplant recipient who developed EBV-negative PTLD with HLH.

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CASE PRESENTATION

A 68-y-old female with end-stage renal disease due to hypertension and diabetes without prior transplantation underwent an uneventful kidney transplant from a deceased donor. The kidney donor profile index was 43%, and both donor and recipient were anti-EBV immunoglobulin G (+) and anti-cytomegalovirus (CMV) (+). Donor-specific antibodies were present: DQ4 (mean fluorescent intensity: 1803) B13 (mean fluorescent intensity: 3533).

Immunosuppression

Induction

Thymoglobulin (4 mg/kg) and solumedrol (500 mg) were used for induction immunosuppression. Additionally, intravenous immunoglobulin (1 g/kg) was administered pretransplant.

Maintenance

A triple drug regimen was used for maintenance immunosuppression with 6.10 mg/kg doses of belatacept (Nulojix, Bristol Myers Squibb, New York, NY) over 3 mo transitioned to 5 mg/kg doses every 4 wks, prednisone taper lasting approximately 2 mo and mycophenolate sodium (540 mg q12h) per protocol.

Posttransplant Course

Immediate graft function was present and length of stay was 4 d. Serum creatinine at discharge and 30 d was 7.92 and 1.38 5 mg/dL, respectively. During routine laboratory

workup at 2 mo postoperatively, the patient was found to have CMV and BK viremia (5473 and 25 155 copies/mL, respectively. The mycophenolate dose was reduced from 540 mg twice a day to 360 mg twice a day. Follow-up testing revealed an undetectable CMV level and reduced BK viral load (6318 copies/mL).

Four months after transplantation, the patient presented to the emergency room with a 1-d history of altered mental status and urinary frequency. A urinalysis was positive for leukocyte esterase, but negative for bacteria. The hemoglobin was 8.8 g/dL, white blood cell count was 3000/μL, and serum creatinine was 1.5 mg/dL. Computed tomography of the head and toxicology screen were unremarkable. Ultrasound of the transplanted kidney was without significant abnormalities. The patient was admitted to the hospital for suspected urinary tract infection, blood, and urine cultures were collected, and ceftriaxone and intravenous fluids were started. Urine culture showed <10 000 CFU/mL of *Escherichia coli* susceptible to ceftriaxone and blood cultures were negative. On hospital day 2, she developed worsening altered mental status, pancytopenia (white blood cell 2000/μL, Hb 6.4 g/dL, and platelets 116 000/μL) and lactic acid of 4 mmol/L. She was transferred to the intensive care unit, received 1 unit of packed red blood cells and antibiotic coverage was broadened to meropenem and vancomycin.

The following day, the patient developed fevers, worsening lactic acidosis (8.2 mmol/L), and refractory anemia (Hb 5.7 g/dL) despite blood transfusion. Serum creatinine rose to 1.8 mg/dL. A lumbar puncture was obtained and was unremarkable. A computed tomography of the chest, abdomen, and pelvis demonstrated marked adenopathy, splenomegaly, and liver masses (Figures 1 and 2). EBV DNA was not detected in the blood (<390 copies/mL).

Within hours, she developed worsening respiratory failure requiring mechanical ventilation and hypotension not responsive to fluid resuscitation. Other signs of MOF included coagulopathy (international normalized ratio 1.8), conjugated hyperbilirubinemia (T/D bili 4/2.3 mg/dL), worsening lactic acidosis (10.2 mmol/L), and oliguria. Continuous renal replacement therapy was initiated, and Amphotericin B was started for empiric fungal coverage.

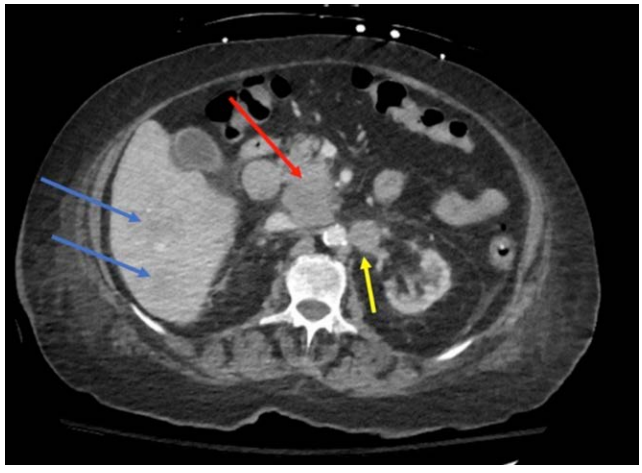

FIGURE 1. Axial view of CT Abdomen showing multiple intra-abdominal masses and extensive adenopathy consistent with PTLD. Blue arrows: liver metastasis; red arrow: large intra-abdominal mass; yellow arrow: para-aortic adenopathy. PTLD, posttransplant lymphoproliferative disorder.

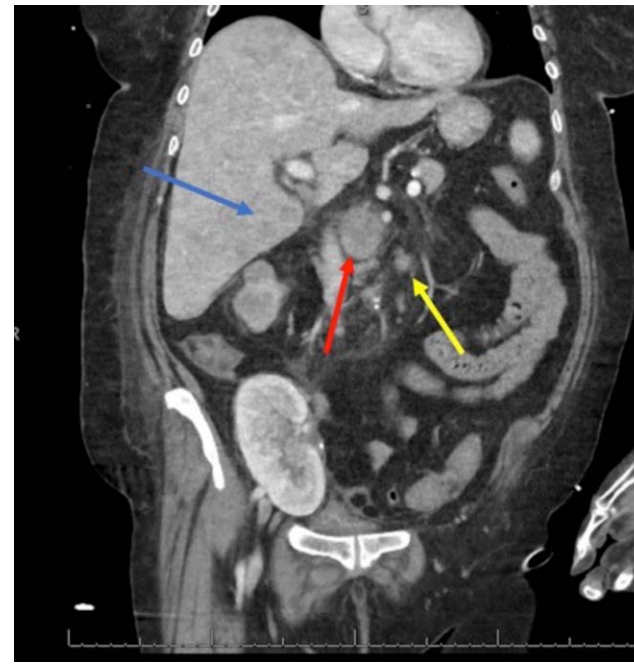

FIGURE 2. Coronal view of CT Abdomen showing multiple intra-abdominal masses and extensive adenopathy consistent with PTLD. Blue arrow: liver metastasis; red arrow: large intra-abdominal mass; yellow arrow: para-aortic adenopathy. PTLD, posttransplant lymphoproliferative disorder.

Additional laboratory values revealed hypertriglyceridemia (863 mg/dL), hypofibrinogenemia (150 mg/dL), and hyperferritinemia (>10 000 ng/mL). Given the clinical and laboratory findings and no clear infectious source identified, HLH in the context of PTLD was suspected. A bedside ultrasound-guided biopsy of a right inguinal lymph node was performed.

Pathology showed large lymphoid cells with irregular nuclei and prominent nucleoli with a moderate amount of vacuolated cytoplasm. Apoptotic and mitotic figures were frequently observed. These cells were positive for CD20 with a proliferation index of >90%. The lymphoid cells were positive for c-MYC (>40%), MUM1 (>30%), BCL2 (>50%), and BCL6 (30%) and negative for CD5, and CD10. In situ hybridization for Epstein-Barr virus encoded small RNA was negative. These findings were consistent with EBV-negative monomorphic diffuse large B-cell lymphoma, PTLD.

Given her poor prognosis and inability to tolerate treatment, the decision was made to withdraw care after discussion with the family. Autopsy confirmed widespread type A1 mononuclear large B-cell lymphoma with diffuse lymph node, pulmonary, and hepatic involvement.

DISCUSSION

This is a rare case of an adult kidney transplant recipient who died postoperatively after developing EBV-negative PTLD with associated HLH. PTLD is a rare but serious complication of organ transplantation that affects approximately 0.5% to 4% of adult renal transplant patients.[2,3] HLH is another rare disease associated with infections and malignancies, such as PTLD, that initiates a hyperinflammatory state in the recipient with subsequent multiorgan failure if not treated promptly.[6] There are few case reports on transplant recipients who developed PTLD with associated HLH.[8-12] However, most reported cases are on EBV (+) PTLD with HLH in pediatric patients undergoing liver or hematopoietic

stem cell transplantation.[9,10] We identified 3 studies in adults undergoing liver and kidney transplantation that also developed EBV (+) PTLD with HLH.[7,11,12] Our patient developed EBV-negative PTLD with HLH post–kidney transplant less than 4 mo after the transplant, which has not been described previously in the literature.

PTLD has the highest rate of occurrence within the first year of transplantation, likely related to the higher degree of immunosuppression in this time period.[13] Although belatacept (Nulojix, Bristol Myers Squibb, New York, NY) has been increasingly used in renal transplantation and was used in our patient, studies have reported an increased risk of PTLD compared to other regimens.[14,15] In one of the largest multicenter randomized controlled trials with this drug (BENEFIT-EXT), 9 out of 359 patients (2.5%) randomized to belatacept and only 1 in 184 patients (0.5%) randomized to cyclosporine developed PTLD in long-term follow-up.[14] The use of belatacept could be one of the reasons that our patient developed PTLD and further studies regarding this association is warranted. EBV infection has been described as one of the main risk factors for PTLD and is found in up to 90% of patients.[16] The primary mechanism described is the EBV-induced proliferation of B cells associated with the decrease in T cell immune surveillance related to the immunosuppression.[2] PTLD has also been described without EBV infection, but its pathogenesis is not clear.[16] EBV-negative PTLD has been associated with worse overall survival than EBV (+) PTLD.[4] Leblond et al reported a median survival of 1 mo in 11 patients with EBV-negative PTLD, significantly lower than the median survival of 37 mo observed in EBV (+) PTLD patients.[4]

HLH is an aberrant hyperferritinemic inflammatory response driven by T cells that can be associated with a fatal cytokine storm.[17] The dysregulation of cytotoxic T lymphocytes and natural killer cells results in dramatic hypercytokinemia, leading to a high level of macrophage activity, causing hemophagocytosis and multiorgan failure associated with this syndrome.[7] The most common HLH triggers are infections and malignancies, such as EBV and lymphoma.[18] In the setting of PTLD, which is commonly associated with EBV infection, the HLH cause might not be clear; however, in the setting of EBV-negative PTLD, like in our patient, malignancy was most likely the main trigger. Our patient also had a recent CMV infection, which has been described with HLH[7]; however, we believe that this was less likely the trigger given that our patient had documented resolution of CMV infection, before her hospital admission. Most of the literature on HLH is from pediatric patients, which can tolerate better the cytokine storm than adults.[6] This condition is associated with a high mortality rate (46%) even in pediatric patients following standard treatment guidelines.[19] The HLH-94 protocol is the most used treatment and combines an intensive therapy of dexamethasone plus etoposide for 8 wks and continuation therapy (if needed) with pulses of dexamethasone plus etoposide and cyclosporine.[19] The overall prognosis of HLH in adults is even worse, with mortality rates ranging from 42-88%.[11]

Only a few cases of PTLD with HLH have been described,[8-12] all on EBV (+) patients. Jha et al reported a pediatric liver transplant recipient that developed PTLD associated with HLH 9 mo after transplantation.[9] The patient responded well to treatment and was doing well at 2-y follow-up.[9] Ali et al also reported pediatric cases in patients undergoing hematopoietic stem cell transplant.[10] In their study, 8 cases of PTLD (2%) were reported, 3 of which died from HLH within 2 mo of transplantation and 1 mo of PTLD diagnosis.[10] Although these were pediatric patients that underwent hematopoietic stem cell transplant and had EBV (+) PTLD, their disease course was similar to our case and highlights how aggressive this condition can be.

Desai et al reported a 55-y-old female with PTLD diagnosed 5 y after a kidney transplant that developed HLH 13 wks following the PTLD diagnosis.[8] The patient did well with treatment and was found to be alive and in remission at 4-y follow-up.[8] Chesner et al reported 1 adult patient who developed PTLD with HLH 16 y after liver transplantation but was recently treated with high dose immunosuppressants for possible recurrent autoimmune hepatitis.[11] The patient developed associated bacteremia and expired from multiorgan failure, likely from septic shock.[11] Karas et al described 2 adult kidney transplant recipients that developed PTLD with HLH diagnosed 8 mo and 15 y after transplantation.[12] The patient with early onset disease survived but developed graft loss, while the late onset patient died despite treatment.[12] Our case differs from these cases in the EBV status and that our patient developed PTLD with HLH much faster than the adult cases described in the literature, highlighting that this can condition can happen even early after transplantation.

CONCLUSION

We described a rare case of an adult kidney transplant recipient who developed EBV-negative PTLD with HLH within 4 mo from transplantation. To our knowledge, this is the first reported case where an adult kidney transplant recipient developed both PTLD and HLH while simultaneously being seronegative for EBV. Given its poor prognosis, physicians need to be mindful of the presentation of PTLD with HLH as a differential diagnosis for sepsis to initiate treatment early and optimize outcomes.

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