Post-transplant Lymphoproliferative Disorder in a Patient After Kidney Transplant, 5-Year Follow-up: A Case Report

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ABSTRACT

Introduction. Post-transplant lymphoproliferative disorder (PTLD) is a serious, life-threatening complication in organ transplant patients receiving immunosuppressive therapy. The risk factors include Epstein-Barr virus infection and a cumulative dose of the immunosuppression.

Case Report. We present a 5-year follow-up case of a 28-year-old patient with PTLD in the gastrointestinal tract. In the ninth month after kidney transplant, the patient was hospitalized for pain in the abdomen and diarrhea. Physical examination demonstrated tenderness in the area of the cecum, and colonoscopy revealed ulcerations in the large intestine. Polymorphic lymphoma (PTLD) was found in the collected samples. The patient received monotherapy treatment with anti-CD20 antibodies, resulting in complete remission of disease, confirmed by computed tomography scan and colonoscopy.

Conclusion. PTLD may have a different clinical course and should be considered in the differential diagnosis of patients after organ transplant.

POST-TRANSPLANT lymphoproliferative disorder (PTLD) is a serious, life-threatening complication in organ transplant patients receiving immunosuppressive therapy [1]. Epstein-Barr virus (EBV) plays an important role in the etiology of PTLD and is found in more than 90% of patients with PTLD, usually as a consequence of the immunosuppressive treatment. The stronger the immunosuppression and the higher its cumulative dose, the greater risk the patient has of developing lymphoproliferative disorders [2,3].

PTLD may have a varied clinical course, resembling infectious mononucleosis with manifestation such as fever, pharyngitis, tonsil enlargement, lymphadenopathy, or may take on fulminant forms characterized by severe metabolic acidosis, graft and other internal organs dysfunction, where infiltrates may take the form of a tumor [4,5]. This paper presents a 5-year follow-up of a patient with PTLD in the gastrointestinal tract.

A CASE REPORT

A 28-year old patient with tubulointerstitial nephritis (chronic self-catheterization due to the posterior urethral valve) who had been hemodialyzed since September 2012 and received a kidney transplant from a deceased donor in July 2013. He obtained immunosuppressive treatment: tacrolimus, mycophenolate mofetil, and prednisone. After kidney transplant, the patient manifested recurrent urinary tract infections (UTIs) caused by multiresistant strains, requiring antibiotic therapy (meropenem, imipenem and cilastatin), and experienced repeated relapses of *Clostridium difficile* infection treated with metronidazole, vancomycin, and then fidaxomicin. Because of the high risk of cytomegalovirus (CMV) infection (CMV donor + CMV recipient -), valganciclovir prophylaxis was used, and early conversion from mycophenolate mofetil to everolimus was performed.

In March 2014, the patient was hospitalized for pain in the abdomen and diarrhea. Physical examination demonstrated tenderness in the area of the cecum. In biochemical tests, hemoglobin was 11.2 g/dL, white blood count was 4390/μL, creatinine was 138 μmol/L, lactate dehydrogenase increased up to 1002 U/L (normal values 240-480), and in a hybridization study in situ for

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EBV infection, numerous positive cells were shown. Colonoscopy revealed ulcerations in the large intestine and polymorphic lymphoma (PTLD) was found in the collected samples. In order to assess the stage of the disease, positron emission tomography–computed tomography (PET-CT) examination was performed, which demonstrated metabolically active areas within the large intestine and especially in the rectum in the form of thickening of the posterior and right-sided wall up to 25 mm in the area of 38 × 21 × 90 mm. Clinical stage IVA, according to the Ann Arbor classification, was determined.

Because of the diagnosis of PTLD, the existing immunosuppressive treatment was modified by gradually reducing tacrolimus (to a blood concentration of 3-4 ng/mL) and then discontinuing it, while continuing the administration of everolimus (concentrations from 5.4-10.2 ng/mL) and methylprednisolone.

In the Department of Hematology, the patient received monotherapy treatment with anti-CD20 antibodies according to the protocol of the Polish Lymphoma Research Group. At the beginning, 4 doses of rituximab (375 mg/m^2 every 1 week) were given, and then maintenance treatment with rituximab (4 doses every 3 weeks) was administered. After a few weeks of treatment, a complete remission was achieved. The patient was carefully followed up by a hematologist under the following schedule: every 3 months for 1 year, every 6 months for 2 years, and then once a year.

Complete remission of disease was confirmed in CT scan and colonoscopy. In the following years (2016 and 2017), 2 episodes of symptomatic UTI were observed (*Klebsiella pneumoniae* extended spectrum beta-lactamase positive–treated with good clinical response to broad-spectrum antibiotics). Currently, more than 5 years from the onset of PTLD symptoms, the patient is in full remission with a very good general condition, sterile urine cultures, stable graft function, and the following laboratory values: creatinine levels 137 μmol/L, estimated glomerular filtration rate 57 mL/min/1.73 m^2, uric acid 271 μmol/L, sodium 138 mmol/L, potassium 3.82 mmol/L, magnesium 0.80 mmol/L, calcium 2.34 mmol/L, alanine transaminase 31 U/L, cholesterol 5.9 mmol/L, leukocytes 5820/μL, erythrocytes 5,080,000/μL, hemoglobin 14 g/dL, and platelets 218,000/μL. Five to 10 leukocytes were observed in urine sediment at the last testing. Currently, the patient receives the following treatment: everolimus 2 mg twice daily, methylprednisolone 4 mg once daily, potassium chloride 391 mg twice daily, betaxolol 20 mg in the morning, atorvastatin 20 mg at night, vitamin B6 and magnesium twice daily one tablet, and fosfomycin 3 g every 2 weeks (as prevention of UTI).

DISCUSSION

PTLD is a heterogeneous group in which uncontrolled lymphocyte proliferation is observed in transplant recipients undergoing chronic immunosuppression [5,6]. Proliferation affects B lymphocytes in more than 85% of cases and is associated with EBV infection. In 15% of cases, hyperplasia involves T lymphocytes, and it affects NK (natural killer) cells extremely rarely. PTLD occurs after both bone marrow and solid organ transplantation, and the type of transplanted organ and the type of the employed immunosuppression appear to have a significant impact on the occurrence of the disease. PTLD occurs most often after heart-lung transplant (5%-10%); occurs less often after heart (3.9%-5%), liver (2.3%), and kidney (0.3-3%) transplant; and occurs the least frequently after bone marrow transplant [3,7,8]. A low 5-year cumulative incidence of PTLD after solid organ transplantation (0.96%) was observed in a Swiss transplant cohort study [9].

As mentioned in the introduction, an infection with EBV usually plays a crucial role in the etiology of PTLD as a consequence of the immunosuppressive treatment. Our patient's infection with this virus has been documented during the diagnosis of PTLD. EBV is a DNA virus that belongs to the Herpes family. A decreased cytotoxic activity of T lymphocytes following immunosuppression allows for reactivation and replication of the virus and tumor transformation of B lymphocytes. Particularly, increased proliferation of infected B lymphocytes can be observed in seronegative recipients in whom primary EBV infection developed after transplantation [2,5,10]. A patient with a primary EBV infection is therefore at a much higher risk of developing PTLD than an individual demonstrating reactivation of persistent infection [8]. The highest risk is manifested by seronegative recipients who have received a seropositive donor organ (D+/R-). The risk of developing PTLD may be further increased in the presence of co-infection with an immunomodulatory virus such as CMV [1,2,8].

At the time of dual immunosuppressive regimens (azathioprine and oral steroids in the 1990s), PTLD was an extremely rare complication. Its incidence began to increase since the introduction of cyclosporin A, tacrolimus, and medications used in induction and treatment of acute transplant rejection such as antithymocyte globulin and monoclonal antibody for CD3 receptor (OKT3) [11,12].

An increased risk of PTLD development occurs mainly in the first year after transplantation [4,7]. Opelz et al [6] evaluated more than 50,000 patients after heart or kidney transplant found a significantly higher incidence of B-cell PTLD in the first year after transplantation, while T-cell PTLD should be expected 5 years after transplant. In another report based on the analysis of data of 1176 kidney recipients, the average time of PTLD occurrence was 72.8 ± 56.3 months after transplant [5].

PTLD can have a variable clinical course and location. The lymph nodes are most often affected, followed by the abdominal cavity (gastrointestinal tract, liver, transplanted organ) and the central nervous system, as well as bone marrow and skin. Lymphoproliferative disorders may also manifest as isolated fever without associated local symptoms. PTLD can occur in the form of a tumor mass or infiltrate as in our patient in the intestine [13]. Gastrointestinal involvement can cause life-threatening ulcers and perforations [14]. Extra-node localization is very common, especially in lymphoproliferative disorders originating from T cells, which are generally aggressive, demonstrate poor response to treatment, and are therefore burdened with a poor prognosis [4,11].

The diagnosis of PTLD requires a great deal of insight because the disease is often insidious and occurs in an extranodal location. The diagnosis is determined by the histopathology of the removed lymph node or specimen

taken from the affected organ through biopsy. It is also helpful to demonstrate the immunoreactivity of EBV protein in lymphocytes [10,11,15].

In the treatment of PTLD, the reduction of immunosuppression is important because immunosuppressive agents impair the function of, among others, cytotoxic T lymphocytes, favoring EBV infection [3,11]. The key role in the treatment of patients with PTLD is played by the chimeric monoclonal antibody directed against the CD20 antigen, rituximab. The administration of rituximab causes rapid elimination of B lymphocytes from the circulation. This is due to complement activation and antibody-dependent cellular cytotoxicity. In addition, rituximab acts synergistically with conventional chemotherapy, sensitizing cells to apoptosis, by inhibiting BCL-2 protein expression, which improves the effectiveness of chemotherapy. The overall response to rituximab used as monotherapy as the first-line treatment is estimated to be around 45% to 50%. It is usually used at a dose of 375 mg/m^2 once a week for 4 weeks, provided that CD20 + (> 90% PTLD) is present [16]. Rituximab is also used as a pretreatment to prevent the development of PTLD in patients infected with EBV [17].

The prognosis in PTLD depends on the type, malignancy features, and stage of the disease. Mortality in monoclonal malignant forms of PTLD is high and can be up to 80%. Polymorphic forms have a better prognosis than monomorphic ones. Adverse prognostic factors are high-grade lymphoma histology and advanced disease in the Ann Arbor classification, central nervous system and bone marrow involvement, disseminated form of the disease (at least 2 extra-node locations), hypoalbuminemia, hepatitis B or C infection, late PTLD, age older than 60 years, and positivity toward cancer before transplant [3,4]. A multicenter study in a group of 80 solid organ transplant recipients diagnosed with PTLD found a 3-year progression-free survival and overall survival of 57% and 62%, respectively. Another prospective study in a group of 230 patients diagnosed with PTLD after kidney transplant found that 73% of the patients survived 1 year after the diagnosis and 61% survived 5 years [4,5].

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