Large Granular Lymphocytic Leukemia Presenting Late After Solid Organ Transplantation: A Case Series of Four Patients and Review of the Literature

A. Katariaa,*, E. Cohena,b, E. Saada, E. Atallahc, and B. Bresnahan

aDivision of Nephrology, Medical College of Wisconsin, Milwaukee, Wisconsin; bDivision of Medicine, Veterans Administration Zablocki Medical Center, Milwaukee, Wisconsin; and cDivision of Hematology, Medical College of Wisconsin, Milwaukee, Wisconsin

ABSTRACT

Post-transplantation lymphoproliferative disorder (PTLD) is a significant complication of solid organ transplantation. Most PTLD is of the B-cell subtype, although T-cell subtype PTLD uncommonly occurs. T-cell PTLDs are usually aggressive neoplasms and shorten patient and allograft survivals significantly. We present a single-center case series of 4 patients who developed T-cell large granular lymphocytic (LGL) leukemia, a rare T-cell PTLD characterized by large granular lymphocytes that have characteristic azurophilic granules and a highly variable clinical course.

DE NOVO development of lymphohematologic malignancies after solid organ transplantation is a significant problem in solid organ recipients, and the majority of them are B-cell subtype post-transplantation lymphoproliferative disorders (PTLDs) associated with an infection with the Epstein-Barr virus (EBV) [1,2]. T-cell PTLD accounts for ~5% of all PTLDs encountered after solid organ transplantation [3]. They generally have an aggressive clinical course [4], but one particular subtype, large granular lymphocytic (LGL) leukemia, is considered to be of a relatively indolent type [5,6]. LGLs normally account for 10%–15% of the circulating lymphocytes and characteristically have an abundant cytoplasm with azurophilic granules. LGL leukemia is predominantly composed of clonally expanded CD3+ LGLs that are activated cytotoxic T cells, although very rarely they are of the CD3− natural killer (NK) cell subtype. We present a single-center case series of 4 solid organ transplant recipients with T-cell LGL leukemia presenting late in the post-transplantation period (Table 1).

CASE 1

A 69-year-old woman with a history of hepatitis C cirrhosis and diabetic nephropathy received a combined liver-kidney (CLK) transplant in 2006. Her immunosuppression regimen consisted of tacrolimus and prednisone. She presented in 2012 with chronic macro-ovalocytic anemia for 4 months. She became transfusion dependent with hemoglobin ranging from 7 g/dL to 8 g/dL with an initial white blood cell (WBC) count that was normal at 7.8 × 10⁹/L with 273 × 10⁹/L platelets. She had normal folate and vitamin B₁₂ levels, and her viral studies were negative for EBV and parvovirus in blood. A peripheral smear showed a differential leukocyte cell count composed of 70% lymphocytes with a predominance of LGLs and a low reticulocyte count of 0.03%. Her bone marrow examination showed hypercellular marrow infiltrated with LGLs that were CD3+, CD8+, CD56−, and CD57+. The patient was subsequently treated with oral cyclophosphamide for 9 months and she had good hematologic response, with hemoglobin stabilizing at 10 g/dL. She continued to have stable kidney and liver allograft function.

CASE 2

A 48-year-old man with a history of focal segmental glomerulosclerosis (FSGS) received a living-donor kidney transplant in 1998. He was on triple immunosuppression with tacrolimus, azathioprine, and prednisone. He was referred to a hematologist in 2012 because of chronic anemia. The initial hemoglobin upon presentation was 7.0 g/dL with a normal WBC count of 6.8 × 10⁹/L and platelet count 424 × 10⁹/L. A peripheral smear showed preponderance of LGLs (absolute lymphocyte count 75%). He had evidence of hemolysis with a serum haptoglobin of <10 mg/dL with a

*Address correspondence to Ashish Kataria, 2643 Hudson Lane GTB Nagar Delhi India 110009. E-mail: ashkats2003@yahoo.com
normal direct Coombs test. A parvovirus polymerase chain reaction (PCR) was negative, and he underwent a bone marrow examination that showed infiltration of intrasinusoidal areas with CD3+ gamma-delta LGL cells with T-cell gene rearrangement suggestive of clonality. He became transfusion dependent and was treated with a 9-month course of oral cyclophosphamide during which his azathioprine was stopped. He had good hematologic response to cyclophosphamide, with hemoglobin stabilizing at 10–11 g/dL without blood transfusion. Unfortunately, he developed late-onset Banff grade 1b cellular rejection in the 9th month of his treatment and progressed to end-stage-renal disease despite treatment with intravenous corticosteroids and antithymocyte globulin. He was on peritoneal dialysis while his hemoglobin remained stable at 10 g/dL at 19-month follow-up.

CASE 3
A 55-year-old man with history of postinfectious glomerulonephritis received a living-donor kidney transplant in 1988. His immunosuppression regimen consisted of cyclosporine and prednisone. In 2008, he developed chronic anemia in 2009 with hemoglobin of 7.3 g/dL and WBC count of 6.4 x 10^9/L at presentation. A peripheral smear showed lymphocytosis (differential lymphocyte count 8.5% of cases) or rarely NK cells (15% of cases) and low reticulocyte count (0.21%). A bone marrow examination showed presence of an aberrant population of LGLs that showed a phenotype of activated T cells (CD3+, CD8+, CD56, CD57+) and normal platelet count of 302 x 10^9/L on presentation. A peripheral smear showed abundant LGLs. Lymphocytosis (differential lymphocyte count 56%), and low reticulocyte count (0.21%). A bone marrow examination showed presence of an aberrant population of LGLs that showed a phenotype of activated T cells (CD3+, CD8+). He initially responded with increased doses of ESA but later became transfusion dependent in 2010. He was started on oral cyclophosphamide with only a partial response and gradually developed iron overload due to multiple blood transfusions, with a serum ferritin of 3,780 ng/mL, requiring chelation therapy. Subsequently, he developed progressive autoimmune thrombocytopenia and continued to be transfusion dependent despite therapies such as splenectomy, rituximab, and antithymocyte globulin. His allograft function deteriorated, with a creatinine of 3.3 mg/dL.

CASE 4
A 46-year-old man with history of FSOS received a living-donor kidney transplant in 1988. His immunosuppression regimen consisted of cyclosporine and prednisone. He developed chronic anemia in 2009 with hemoglobin of 7.3 g/dL and WBC count of 6.4 x 10^9/L at presentation. A peripheral smear showed lymphocytosis (differential lymphocyte count 4.5 x 10^9/L) with an elevated number of LGLs and normal platelet count of 302 x 10^9/L. A bone marrow biopsy showed abnormal presence of increased LGLs that were CD3+ along with CD8+, CD16+, and CD57+. There was suggestion of clonality by the presence of T-cell gene rearrangement. In addition, an aberrant population of NK cells that were CD3−, CD4+, CD56+, and CD16+ was noted. PCR for EBV was negative. This T-cell and NK-cell LGL leukemia was refractory to treatment with oral cyclophosphamide, weekly methotrexate, and antithymocyte globulin. The patient remained transfusion dependent but had good kidney allograft function.

DISCUSSION
An undesirable effect of the immunosuppression used in solid organ transplantation is the loss of innate defense mechanisms that prevent development of cancer, especially lymphoproliferative disease [7,8]. The proliferation of both T and B cells is initially polyclonal and is targeted specifically against the allograft antigens, but often it becomes unrestricted, perhaps owing to “second hits” such as EBV infection, and then becomes monoclonal and malignant [7–9]. LGL leukemia is a clonal disorder of activated T cells (>85% of cases) or rarely NK cells (<15% of cases) and...
accounts for ~2%–5% of chronic lymphoproliferative disorders in North America [6]. Its prevalence in the solid organ transplant setting is unknown. In our review of the literature, the present report is the largest series of subjects developing LGL leukemia after solid organ transplantation [10–12].

Typically, T cell LGL leukemia affects middle-aged adults (median age, 55 years) with an indolent and often asymptomatic course [13]. The diagnosis is made by the over-abundance of typical large lymphocytes in blood with abundant cytoplasm and azurophilic cytoplasmic granules. These cells have phenotypic markers of activated T cells, such as CD3+, and commonly CD8+, CD4−, and CD57+, and a significant association with EBV has not been found [5,14]. Lymphocytosis and neutropenia is present in most patients, and pure red cell aplasia occurs less frequently [13,15]. Other associated abnormalities described in T-cell LGL leukemia are Coombs-positive hemolytic anemia, various autoimmune disorders [12,16], and monoclonal gammopathies [14,17]. Bone marrow examination may show hypercellularity and often has intrasinusoidal infiltration with lymphocytes and variably preserved or diminished erythroid and megakaryocytic precursors [5]. Immunochemical analysis is necessary for the diagnosis of T-cell LGL leukemia [13,14]. Lymphocytes are typically CD3+ and show phenotypic markers of activated T cells. A rare subtype, CD3− LGL, contains clonal expansion by NK cells. This subtype is shown to have a more aggressive clinical course, a higher association with EBV, and a dismal outcome [14,18–20].

The general indications of treatment of LGL leukemia are severe neutropenia with recurrent infections, severe refractory anemia, and severe thrombocytopenia [13,14]. There are no formal trials in solid organ recipients guiding the specific management options for LGL leukemia. A reduction in immunosuppression is generally advisable in solid organ transplant recipients with T-cell PTLD (3), but there is no evidence to support that this strategy works in LGL leukemia. In the nontransplant setting, cyclophosphamide, cyclosporine, and methotrexate have been used with variable success as first-line agents [21–23], and alemtuzumab and antithymocyte globulin have been proposed for refractory disease [24,25]. It is ironic that our patients developed LGL leukemia despite being on calcineurin inhibitors for their kidney transplant immunosuppression and cyclosporine is considered to be one of the effective first-line agents for LGL leukemia in the nontransplant setting. Only anecdotal reports of allogeneic stem transplantation are present in the literature and its efficacy is unknown [26]. Combination chemotherapy is generally ineffective [13,27].

In our series, all 4 patients developed severe transfusion-dependent anemia and none had infection with parvovirus or EBV. All of the patients developed LGL leukemia many years after the transplantation. Gentile et al reported 3 cases of LGL leukemia after renal transplantation and observed a similar delayed onset [10]. Similar observations were reported by Masuda et al and Stamatopoulos et al in 2 separate case reports [11,12]. Two of the 4 patients in our series had substantial hematologic response with oral cyclophosphamide therapy, and at the time of writing 3 of the patients had stable allograft function and 1 patient lost the allograft owing to delayed cellular rejection. In our review of earlier literature of organ transplant recipients with T-cell LGL leukemia, oral cyclophosphamide has been used with good results in 2 patients [10,11]. Each of our patients was surviving at the follow-up period of 14–67 months. This is similar to the minimum survival period of 20 months reported by Gentile et al [10]. The reported median survival period in the general population has been reported to be >10 years [28].

In summary, LGL leukemia in solid organ transplant recipients usually presents late in the transplant period and has a variable clinical course, ranging from an indolent behavior to refractory cytopenias, and has a variable response to chemotherapeutic agents. LGL leukemia should be kept in mind during the evaluation of a solid organ transplant recipient who develops refractory anemia many years after the transplantation.

REFERENCES


