CHEST

A 48-Year-Old Man With Leukopenia, Jaundice, and Skin Rash After Lung Transplantation

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A 48-year-old African-American male subject presented with progressive fatigue, jaundice, and new-onset leukopenia 12 weeks after undergoing bilateral lung transplantation for advanced pulmonary sarcoidosis. His transplant surgery and immediate posttransplantation course were uneventful. Induction immunosuppression included methylprednisolone 500 mg intraoperatively and basiliximab (anti-IL-2 monoclonal antibody) on days 0 and 4 after transplantation. His maintenance immunosuppression posttransplantation was prednisone 20 mg daily, tacrolimus with target tacrolimus levels 10 to 15 ng/mL, and mycophenolate mofetil 750 mg twice daily. Both the donor and recipient were seropositive for cytomegalovirus and Epstein-Barr virus. Infectious disease prophylaxis consisted of valganciclovir, trimethoprim/sulfamethoxazole, and voriconazole. Results of the surveillance bronchoscopy conducted after the lung transplant were negative for acute cellular rejection or infection at 4 and 12 weeks' posttransplantation. Findings on spirometry had continuously improved since transplantation.

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Physical Examination and Diagnostic Studies

The patient was afebrile with stable hemodynamics and oxygen saturation of 99% on room air. His physical examination was unremarkable except for jaundice. Laboratory evaluation was notable for a WBC count of 0.2×10^9/L. Hemoglobin and platelet count were stable and within normal range. Liver panel was notable for alanine transferase 161 U/L (normal, 7-53 U/L), aspartate transferase 112 U/L (normal, 11-47 U/L), alkaline phosphatase 624 U/L (normal, 38-126 U/L), and bilirubin 6.3 mg/dL (normal, 0.3-1.1 mg/dL). Levels of serum electrolytes, BUN, and creatinine, as well as the hemolysis panel, were within normal ranges. Four weeks previously, the WBC count was 5×10^9/L and levels of liver enzymes and bilirubin were normal. His chest radiograph was clear.

The patient's leukopenia and jaundice were initially attributed to side effects of medications. Mycophenolate mofetil and valganciclovir were held because of leukopenia, while trimethoprim/sulfamethoxazole and voriconazole were discontinued due to the abnormal liver enzyme levels. Laboratory assessments were all negative for viral, bacterial, and fungal infections, including hepatitis A, B, and C, rotavirus, and parvovirus B19 serologic findings; whole blood polymerase chain reaction for cytomegalovirus (CMV),

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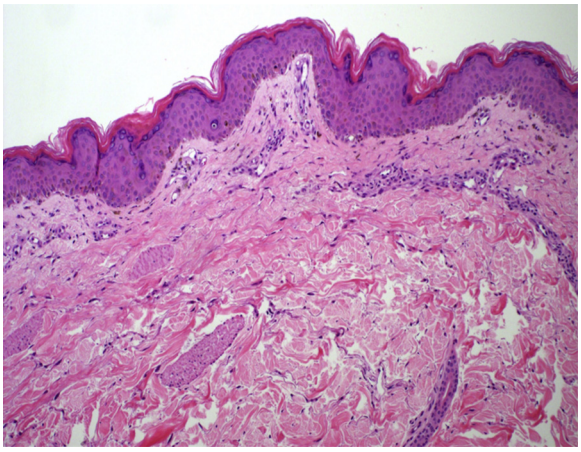

Figure 1 – *Skin biopsy specimen showing superficial perivascular lymphocytic infiltration within the dermis.*

Epstein-Barr virus (EBV), adenovirus, and human herpesvirus 6 and 8; serum galactomannan; and urine histoplasmosis antigen. His liver ultrasound was unremarkable.

Despite holding use of potentially harmful medications, and daily administration of granulocyte-colony stimulating factor, the patient's leukopenia progressed to pancytopenia over the next 10 days. A bone marrow biopsy was performed, and the results showed hypocellular bone marrow consistent with bone marrow aplasia; results of a liver biopsy were suggestive of drug-induced hepatopathy. During this time, the patient developed a pruritic maculopapular rash on his extremities and severe diarrhea. A skin biopsy specimen revealed superficial perivascular lymphocyte infiltrates within the dermis (Fig 1). Peripheral blood short tandem repeat (STR) analysis revealed chimerism with 99% of T lymphocytes (T cells) of donor origin.

What is the diagnosis?

Diagnosis: Graft-vs-host-disease after lung transplantation

Discussion

Presence of donor lymphocytes in the recipient blood circulation early after solid organ transplantation (SOT) is not uncommon, and it may play a role in organ tolerance. However, persistence of donor lymphocytes in association with evidence of engraftment in organs such as skin, gastrointestinal tract, liver, and bone marrow are the principal features of graft-vs-host-disease (GVHD). Although GVHD is a common complication after allogeneic hematopoietic stem cell transplantation (HSCT), it is rare after SOT, likely due to a markedly lower donor lymphocyte burden associated with SOT compared with HSCT. In keeping with this theory, GVHD is more common after transplantation of organs with greater amounts of lymphoid tissue such as the liver and small bowel compared with the kidney, heart, and lung. To date, only four other cases of GVHD after lung transplantation, and six cases after heart/lung transplantation, have been reported.

A greater degree of human leukocyte antigen (HLA)-matching between the donor and recipient has been considered as the main risk factor for development of GVHD after SOT. If alloreactive T cells from the graft express shared HLA determinants with the donor, they are less likely to be destroyed by the recipient immune system, and they will have a higher chance of engraftment. However, the patient in our study received a 2A, 2B, 1DR HLA-mismatch allograft, of which there was HLA identity at only one of six loci to the donor. Therefore, a high degree of HLA conformity as a risk factor for development of GVHD was not applicable in our case.

SOT recipients who were immunosuppressed prior to transplantation seem to be at greater risk for GVHD following transplantation. This scenario may facilitate the engraftment of competent donor T cells. As such, many cases of GVHD after SOT have occurred in chronically immunosuppressed patients who had undergone a second or third SOT. To date, a link between sarcoidosis and the development of GVHD after transplantation has not been established. The underlying T-cell dysregulation in patients with sarcoidosis, and more specifically dysfunctional T-regulatory cells, in combination with a proinflammatory TH1 cytokine milieu in a recipient with sarcoidosis can be conducive to proliferation of the donor T cells that are activated by mismatched recipient cells.

The patient in our study was taking prednisone 10 mg daily with no additional immunosuppressive agents prior to transplantation.

GVHD after SOT usually presents with fever, skin rash, diarrhea, abnormally liver enzyme levels, and bone marrow suppression. Macrochimerism (the presence of $>$ 1% of donor T cells) occurs commonly in the first few weeks after transplantation even in the absence of GVHD. However, persistence of macrochimerism and evidence of donor T-cell engraftment are the foundation of GVHD. Macrochimerism should resolve after the first few weeks following the transplant. It is possible that in susceptible individuals with a dysregulated immune response, chimerism may go on to cause donor T-cell engraftment. Hence, GVHD can be suspected in a symptomatic patient with demonstration of donor lymphocyte chimerism (by leukocyte STR) beyond the first few weeks following SOT. Alternatively, if the sex of the donor differs from the recipient, then fluorescence in situ hybridization analysis of sex chromosomes in lymphocytes from peripheral blood, bone marrow, or a skin biopsy specimen can be diagnostic.

The optimal treatment of GVHD after SOT remains unclear and has been largely extrapolated from experiences with GVHD after HSCT. The first line of therapy has usually consisted of immunosuppression augmentation with methylprednisolone 2.5 mg/kg/d. Therapeutic options beyond steroids have included either further immunosuppression by using anti-T-cell antibodies or cytokine inhibitors (eg, anti-IL-2, anti-tumor necrosis factor α), or decreased immunosuppression, in an effort to enhance the recipient immunity to reject donor lymphocytes.

The outcome of GVHD after SOT is generally poor, with mortality exceeding 80%. In most cases, death is a result of sepsis, bone marrow failure, and multiorgan failure. Favorable outcomes are generally associated with milder disease and/or early diagnosis before development of bone marrow aplasia. Of the two lung transplant recipients who survived, one had mild leukopenia (WBC count, 1.2×10^9/L), and GVHD in the second case was limited to skin, with no bone marrow involvement. Both cases responded to augmentation of immunosuppression with methylprednisolone 2.5 mg/kg/d. Because the manifestations of GVHD are nonspecific and similar to findings seen with more common entities such as drug reactions and infections, diagnosis and treatment are often delayed.

TABLE 1] Laboratory Values Before and After ATG Therapy

Laboratory Test	At Presentation	2 Weeks After ATG and G-CSF
WBC count	0.2×10^9/L	4.5×10^9/L
Hemoglobin	6.8 g/dL	9.5 g/dL
Platelets	41×10^9/L	184×10^9/L
AST	112 U/L	35 U/L
ALT	161 U/L	94 U/L

ALT = alanine transaminase; AST = aspartate transaminase; ATG = anti-thymocyte globulin; G-CSF = granulocyte-colony stimulating factor.

Clinical Course

Initial therapy with steroids (methylprednisolone 2.5 mg/kg/d) was unsuccessful in the study patient, with no improvement in pancytopenia, diarrhea, skin rash, or abnormal liver enzyme levels. Because the patient had already received basiliximab at the time of transplantation, we decided to use a T-cell-depleting strategy instead of cytokine inhibition. Thus, a 4-day trial of anti-thymocyte globulin at 1.5 mg/kg was started, followed by granulocyte-colony stimulating factor infusion. Fourteen days later, the patient had significant clinical improvement with complete resolution of his skin rash, diarrhea, and pancytopenia (Table 1). Results of a repeat STR at this time showed complete resolution of the donor chimerism. Over the next month, the patient developed CMV, EBV, and human herpesvirus 6 viremia. His case was further complicated by a recurrence of bone marrow failure. Peripheral blood STR showed relapse of GVHD. The patient continued to deteriorate and ultimately died of septic shock and multiorgan failure on day 163 posttransplantation.

Clinical Pearls

1. *GVHD after lung transplantation presents as nonspecific symptoms of fever, diarrhea, skin rash, and bone marrow failure.*
2. *The milder and more limited manifestations of the disease are often misinterpreted as medication side effects or viral infections, delaying diagnosis.*
3. *Early diagnosis (with STR or fluorescence in situ hybridization) before the disease establishes itself with bone marrow aplasia may be the key to successful treatment.*
4. *GVHD is associated with a high mortality rate; death is usually attributable to sepsis complicating bone marrow failure.*

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Suggested Readings

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