Transfusion-associated graft-versus-host disease in a liver transplant recipient: an unusual presentation and review of the literature


BACKGROUND: Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, nearly universally fatal complication from transfusion of nonirradiated cellular blood components, occurring when a recipient’s immune system is unable to recognize and destroy transfused T lymphocytes. Irradiation of cellular components eliminates this risk. We present an unusual case of a liver transplant recipient developing TA-GVHD 13 weeks after transfusion of a random unit of nonirradiated red blood cells (RBCs) that happened to be from a donor homozygous for an HLA haplotype shared by the patient.

STUDY DESIGN AND METHODS: This study was a single case review of a liver transplant recipient who developed skin GVHD and marrow aplasia. Clinical course and the chimerism studies involving the patient, the liver donor, and the blood donor are detailed.

RESULTS: The patient presented 3 months posttransplant with GVHD of his skin and marrow aplasia. In addition to standard antigraft immunosuppression, this patient had started the interleukin-1 receptor antagonist anakinra on Posttransplant Day 13 for an acute gout flare. Chimerism studies on the patient’s peripheral blood identified a population of CD3 cells that did not originate with either the patient or his liver donor. HLA studies and microsatellite profiling of the unknown CD3 population identified the source of the patient’s TA-GVHD, a unit of nonirradiated, nonleukoreduced apheresis RBCs.

CONCLUSION: Use of an immunomodulating agent may have contributed to the development of TA-GVHD in a liver transplant patient who received a random unit of nonirradiated RBCs by chance from an unrelated haploidentical donor.

ABBREVIATIONS: STR(s) = short tandem repeat(s); TA-GVHD = transfusion-associated graft-versus-host disease.

We present the case of transfusion-associated graft-versus-host disease (TA-GVHD) in a 59-year-old group A D– male approximately 90 days status postorthotopic liver transplant for hepatitis C virus. The patient had a past medical history significant for chronic renal disease, Type 2 diabetes, hypertension, and gout, for which he took allopurinol and colchicine. He received a deceased donor liver from a 52-year-old group A D+ woman. Before, during, and after the transplantation, the patient received numerous acellular and cellular blood components (40 units of RBCs, 27 units of plasma, three doses of platelets [PLTs], and five pools of cryoprecipitate). RBCs and PLTs were not ordered as irradiated as it is not considered standard practice to irradiate cellular blood components for solid organ transplant recipients; however due to inventory concerns, some of the cellular products issued happened to be irradiated. Once the patient was deemed a liver transplant candidate, all cellular products were ordered to be leukoreduced to prevent HLA alloimmunization. During an episode of massive upper gastrointestinal bleeding on the day after admission (and before the patient was deemed a liver transplant candidate), the...
The patient received 5 units of emergency-release RBCs (3 A D− and 2 O D−), only one of which was leukoreduced and irradiated (the remaining four were neither leukoreduced nor irradiated). The last units of red blood cells (RBCs) and PLTs were transfused 11 days after transplant. The patient received all transfusions at his transplant facility. His posttransplant immunosuppressive regimen consisted of induction with antithymocyte globulin followed by mycophenolate mofetil and tacrolimus with bactrim prophylaxis. His immediate postoperative course was complicated by acute on chronic renal failure, biliary stent placement, and acute gouty flare while on allopurinol and colchicine. Allopurinol and colchicine were discontinued and he received treatment with a prednisone taper and injections of the interleukin (IL)-1 receptor antagonist anakinra. The anakinra was prescribed at 100 mg sc qd dosing as needed for acute gouty flares.

Approximately 3 months after the transplant, the patient presented to a local urgent care clinic with a new-onset pruritic, faint, erythematous, maculopapular rash that began on his neck with spreading to his entire body. A complete blood count performed at this presentation revealed leukopenia with an absolute neutrophil count of $540 \times 10^6/L$ (normal range, $1800 \times 10^6-7000 \times 10^6/L$).

The patient was admitted to the transplant facility where his bactrim, mycophenolate mofetil, and anakinra were stopped. Topical triamcinolone and diphenhydramine were provided for immediate relief of his pruritus. The patient’s liver graft function at the time of admission was normal by laboratory markers. However, the patient’s rash worsened and was accompanied by fever. Dermatology and hematology services were consulted. A skin biopsy showed Grade II acute GVHD. Marrow biopsy revealed a hypocellular marrow (20% cellularity) with minimal hematopoiesis consistent with marrow aplasia. Flow cytometry showed CD34-positive progenitor cells to be only 0.1% of the white blood cells (WBCs) present. Chimerism studies of the patient’s marrow and peripheral blood revealed the presence of a population of CD3 cells (approx. 50% of total CD3), which did not originate with either the patient or his liver donor. Upon being informed of this unusual finding, the transfusion service medical director requested that the immunogenetics laboratory identify the HLA type of this population of interest.

With the suspicion that this might be TA-GVHD, allo- geneic hematopoietic stem cell transplantation as a potential cure was offered to the patient, but he declined. In an attempt to suppress the T lymphocytes of unknown origin that were present in the patient’s marrow and peripheral blood, the patient was treated with antithymocyte globulin 11 days before death with the addition 2 days later of alefacept, an LFA3-immunoglobulin fusion protein that binds to CD2 on T-lymphocytes, 2 days later. The patient’s marrow function never recovered. The patient’s clinical course included Clostridium difficile colitis, liver graft failure, candidemia, and vancomycin-resistant enterococcal sepsis. He succumbed to septic shock less than 1 month after admission with the rash. The family declined the request for an autopsy. All cellular blood components transfused since presentation with the skin GVHD were irradiated and leukoreduced.

Before his liver transplant, the patient was heterozygous at the HLA A and B loci (A1, A2, B8, B51). The liver donor was homozygous at the A locus (A2) and heterozygous at the B locus (B7, B51). However, typing of the patient’s CD3 lineage cells performed during his second hospitalization with rash and evidence of GVHD demonstrated homozygosity at both the A and B loci. The CD3 cells typed as A1, B8 with no evidence of host or liver donor A2, liver donor B7, and minimal reactivity for host or donor B51 antigens (Table 1). The results were suggestive of engraftment in the CD3 lineage from an individual homozygous for A1, B8, one of the most common haplotypes in the Caucasian population.12

The investigation to discover the implicated blood product began with identifying the 22 cellular blood components that were transfused, but not irradiated. Seventeen of these donors did not have HLA types on file at our blood collection facility. The first half of these donors were contacted and asked to come in for HLA testing.

Subsequent HLA and short tandem repeat (STR) analysis of these donors resulted in identification of a donor who was homozygous for A1, B8 and whose microsatellite profile matched that of the CD3 cells isolated from patient samples during his final admission. The chimerism test, which analyzes genomic STRs or microsatel-

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<tr>
<th>Source</th>
<th>HLA A locus</th>
<th>HLA B locus</th>
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<tr>
<td>Patient before transplant</td>
<td>A1, A2</td>
<td>B8, B51</td>
</tr>
<tr>
<td>Liver donor</td>
<td>A2, A2</td>
<td>B7, B51</td>
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<tr>
<td>Foreign CD3 cells in blood and marrow</td>
<td>A1, A1</td>
<td>B8, B8</td>
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TABLE 1. HLA A and B typing of the patient, the liver donor, and the foreign population of CD3 cells identified in the patient’s peripheral blood and marrow.
The implicated blood component was a nonirradiated, nonleukoreduced apheresis RBC unit that the patient received 10 days before his liver transplant. This product, which was collected 10 days before transfusion, was one of the 5 units of RBCs ordered for emergent bleeding. The donor of this unit is a 62-year-old male, group O D−, CMV-seronegative, multigallon blood donor. No other component from this donor has been implicated in TA-GVHD.

DISCUSSION

TA-GVHD is one of the most feared adverse events related to blood transfusion. All cellular blood components...
contain viable lymphocytes, even those that have undergone prestorage or bedside leukoreduction. The lymphocytes often remain detectable in the circulation of the transfused immunocompetent recipient for several days and in some instances years, after a transfusion, before finally being removed by the recipient’s immune system. TA-GVHD is thought to develop when the recipient’s immune system does not or cannot recognize donor lymphocytes as foreign and the donor cells engraft and proliferate. These invading T-lymphocytes may target recipient organs, primarily the skin, liver, gastrointestinal tract, and marrow. Fever, rash, hepatitis, and gastroenteritis typically occur 2 to 30 days after transfusion. Pancreatitis leading to death usually occurs 2 to 3 weeks after initial presentation.

We found this case of interest because it has some features that are common to previous case reports of TA-GVHD and some features that are unique. As to the common features, this is the third reported case of TA-GVHD that resulted from a blood donor who was homozygous for HLA haplotype A1 B8, one of the most common haplotypes in the US Caucasian population. As explained by others, factors in addition to the HLA haplotype appear to be important for TA-GVHD. The predicted frequency of TA-GVHD cases that would result based on calculations of HLA haplotype frequencies alone in the US population is far greater than the number of cases that actually occur. For example, Triulzi and colleagues report the expected frequency of transfusion of blood from HLA homozygotes to HLA heterozygotes to be 1:7174 in US Caucasians, although the published rate is far less. Taking our transfusion service as an example, where 800 RBCs per day on average are issued, we would expect to have a case of TA-GVHD every 8 to 10 days. If we estimate that approximately 50% of RBCs are issued irradiated, we still would expect to see several cases a year, but we do not. In 2010, for example, of a total of 40 transfusion-related fatalities reported to the Food and Drug Administration (FDA), there was only one case of TA-GVHD. In the case reported by Triulzi and colleagues, the donor was also homozygous for HLA Class II DR3. As reported by Mack and coworkers the three-locus haplotype A1 B8 DR3 ranks among the top five haplotypes in the European American population. In our case as well as the third case, the Class II was not determined. It is possible that HLA Class II has more bearing on antigen-presenting cells and their ability to engraft in a patient—even an immunocompetent patient—than previously recognized. This small but rising trend of TA-GVHD caused by donors who was homozygous for a shared HLA haplotype may warrant more consideration as to policy changes with regard to these donors (and testing of donors for this haplotype). Given the rarity of these cases, it is neither cost-effective nor feasible from a practical standpoint to make sweeping policy changes at this time. Further study of these donors may help lead to a more thoughtful approach in the effort to prevent further cases of TA-GVHD. Questions presently exist as to the extent of HLA antigen sharing necessary to predispose to TA-GVHD as other factors such as the lymphocyte content of the unit, the age of the unit, and the immune status of the patient has some bearing on whether TA-GVHD is the ultimate result. However, if it had been known before transfusion that the patient was going to receive a cellular component from a donor who was homozygous for a shared HLA haplotype, the unit would have been irradiated.

The unique features of this case include the relatively delayed onset of TA-GVHD and use of an IL-1 receptor antagonist in addition to immune suppression after liver transplantation. These two features may or may not be interrelated, although the timing of the administration of the IL-1 receptor antagonist raises suspicion.

TA-GVHD after solid organ transplantation has been reported in four cases. The cases involving liver transplant patients were reported in the mid-1990s. Clinical features in TA-GVHD after organ transplantation may overlap somewhat with classic GVHD after organ transplantation. In these cases of classic organ transplantation–derived GVHD, the GVHD is caused by the organ donor–derived passenger lymphocytes contained in the transplanted organ exerting an immune response against the recipient’s liver, skin, intestine, and marrow. Clinical features of organ donor–derived GVHD include severe diarrhea, hepatitis, and rash. Organ donor GVHD is also often accompanied by pancytopenia as the marrow is targeted for destruction by these donor organ–derived lymphocytes. In the four published cases of TA-GVHD after organ transplant (as well as our case), the cause of the GVHD was proven to be lymphocytes from a transfused cellular blood component and not passenger lymphocytes from the transplanted organ. The distinction is important.
in regard to outcomes as TA-GVHD has a uniformly dismal mortality rate approaching 100%, while some 25% to 50% of patients suffering from liver organ transplant GVHD have survived.14,18

The immunosuppressive agents used now in liver transplant patients differ in their mechanism of action. The relative paucity of cases of TA-GVHD involving liver transplant recipients since this regimen became standard suggests that the immunosuppression that results is not, by itself, sufficient to predispose to TA-GVHD. The low risk of TA-GVHD after organ transplantation has resulted in the current practice that most transplant centers do not routinely irradiate cellular components unless the patient has an additional underlying condition that would predispose to TA-GVHD.18

Anakinra (brand name Kineret, Amgen, Thousand Oaks, CA) is an FDA-approved drug prescribed for the treatment of rheumatoid arthritis. It has reportedly been used in cases of resistant chronic tophaceous gout.19 This medication is a recombinant, nonglycosylated version of the human IL-1 receptor antagonist prepared from cultures of genetically modified Escherichia coli using recombinant DNA technology. IL-1 is an early-response cytokine that is important at inflammatory foci for cellular activation and the subsequent production of chemokines for the recruitment of WBCs at the site of inflammation.20 IL-1 has been shown to have a positive influence in restoring deficient responses in immunosuppressed individuals and in immune-deficient animal models.20 This cytokine also has been shown to up regulate the production of other chemokines including IL-8, a neutrophil and T-lymphocyte chemotactic cytokine, and macrophage inflammatory protein-1α, a monocyte and neutrophil chemotactic factor.20

The initial dose of anakinra, 100 mg sc qd, was given 13 days after transplant and continued intermittently daily as needed for acute flares until presentation of the skin rash 3 months later. The patient reported good control of the gout flares with anakinra, with resumption of pain within 2 days of stopping this medication. Although the exact mechanism is difficult to postulate, it is possible that this medication allowed the balance to shift to a more T-cell-suppressed state, both for the recipient lymphocytes and for the viable blood donor T lymphocytes, leading to the delayed presentation of TA-GVHD. Alternatively, this medication may have further altered the patient’s immune system in such a way that the patient, who would not otherwise have developed TA-GVHD, was now at much higher risk for doing so. While anakinra should not impact T lymphocytes in the way that for instance fludaribine does, it is possible that it has this effect when combined with a “usual” solid organ transplant immunosuppression regimen.

Universal irradiation of all cellular components in the United States would prevent this unfortunate outcome in all transfusion recipients. However, the extremely low incidence of TA-GVHD, combined with the side effects of the process on the RBC product, and the difficulty of managing a RBC inventory that expires in 28 days have all resulted in the adoption of selected irradiation for known at-risk recipients in the vast majority of American transfusion services. There are several problems with such selective protocols,21 as they are subject to the individual transusing physician’s knowledge of the numerous risks of TA-GVHD22 and their understanding of their patient’s evolving clinical condition. Even the most astute clinician may be led astray by the selective irradiation protocol in the case of a seemingly immunocompetent pediatric patient that has yet to be diagnosed with a congenital immunodeficiency.23-25 Patients on immune system modifiers, such as anakinra, are problematic leading to the question of whether all patients on these drugs be considered another population at risk. Selective irradiation policies will also not prevent transfusion of blood components from randomly selected donors who are homozygous for a shared HLA haplotype1 with an immunocompetent recipient. This is definitely less of a risk in the melting pot of the United States, than in more isolated or homogenous populations, but it does occur as shown in the case described by Triulzi and colleagues and our patient.1

Additional areas of concern if selective protocols will continue to be used are in the transfusion of so-called “fresh” RBCs as a controversial risk factor for TA-GVHD. In a survey of more than 122 cases of TA-GVHD in Japan, 62% were from units not more than 72 hours old.26 The authors postulate that as the RBC units age in the storage temperatures of the refrigerator, the viability of bystander lymphocytes decrease.27 Should experts in the transfusion field determine that fresher RBCs are truly associated with improved outcomes in certain populations then it is incumbent to determine if those fresh units need to routinely be irradiated. Of note, the implicated unit in our patient’s case was 10 days old, which would barely meet the criteria for fresh as defined in the ongoing clinical trial RECESS (NCT 00991341).28 The immunocompetent patient who developed TA-GVHD after receiving RBCs from a donor homozygous for a shared haplotype after cardiac surgery described by Triulzi and coworkers1 received an even “fresher,” 6-day-old unit.

Finally, several factors may have predisposed our patient to this unfortunate outcome. The patient’s postliver transplant immunosuppression regimen could have, when combined with a potent IL-1 receptor antagonist, pushed his immune system toward a more immuno-compromised state. This disruption in our patient’s immune system combined with a relatively fresh, nonleukoreduced, nonirradiated unit of RBCs from a random donor that happened to be HLA haplotypeidentical may have set the perfect storm for TA-GVHD in motion.
CONCLUSIONS

This case is an unusual presentation of TA-GVHD. The patient’s liver transplant, his posttransplant immunosuppressive therapy, and the immunomodulating drug he received to treat his gout all created susceptibility for his immune system to be attacked and destroyed by transfused lymphocytes from one particular donor with a very common HLA type that he happened to share. The rash that heralded this unfortunate outcome occurred 13 weeks after his transfusion, making this a very unusual case. HLA studies were performed on the patient, his liver donor, and a portion of the implicated blood donors, identifying a single responsible donor who had a very common HLA type shared with the patient.

CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES


