Transfusion-associated GVHD: 10 years' experience at the American University of Beirut—Medical Center

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BACKGROUND: Although rare, transfusion-associated GVHD (TA-GVHD) is a fatal complication of blood transfusion in which active lymphocytes from the donor attack and destroy recipient organs and tissues.
STUDY DESIGN AND METHODS: A search of patient records was carried out at the American University of Beirut—Medical Center, looking for patients who developed TA-GVHD over a 10-year period extending from 1991 to 2001. Relevant information was collected and analyzed.
RESULTS: A total of 10 records were found as a result of this search. All were immunocompetent and received fresh nonleukoreduced, nonirradiated blood. The majority received the transfusion at outside periphery hospitals. They received different treatment modalities. The mortality rate was 100 percent.
CONCLUSION: TA-GVHD is a serious complication with very high mortality. Effective prevention guidelines should be established in Lebanon including irradiation and the creation of a central blood bank.

ABBREVIATIONS: CABG = coronary artery bypass graft; TA-GVHD = transfusion-associated GVHD.

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Transfusion-associated GVHD (TA-GVHD) is a rare, but usually fatal, complication of nonirradiated cellular blood elements transfusion. It occurs as a result of engraftment of immunocompetent donor lymphocytes into the recipient. One of the requirements for the development of the disease is the inability of the host to build up an immune response against the donor's cellular elements.[1] This can take place not only in immunocompromised but also in immunocompetent individuals when both the donor and the recipient share HLA antigens. The occurrence of this HLA mismatching is increased when family members are the blood donors.[2] TA-GVHD is often difficult to distinguish clinically from a viral infection or a drug eruption, and it generally does not respond to immunosuppressive therapy. Furthermore, it is almost always fatal with a very rapid and fulminant course.[3]

The presenting symptom is usually fever above 38°C with a median onset time of 10 days.[4] The main body systems affected include the skin, with the appearance of an erythematous maculopapular rash, the liver, as reflected by elevated levels of bilirubin and alkaline phosphatase in addition to abnormal liver enzymes, and the gastrointestinal system where a wide range of complications is possible. Furthermore, pancytopenia is usually the main problem in most cases of TA-GVHD, which differentiates it from allogeneic marrow transplantation-derived GVHD. Severe infections remain the main cause of death in these patients with a very high mortality rate (>90%).[3]

MATERIALS AND METHODS

A search of patient records was carried out at the American University of Beirut—Medical Center, a tertiary care center in Lebanon. We looked up all charts of patients who developed TA-GVHD over a 10-year period extending from 1991 to 2001. Relevant information was collected from the charts using a detailed form. Variables studied included demographic data in addition to clinical data, such as the number of units transfused, the donors, the treatment received, and the final outcome.

RESULTS

A total of 10 records were found as a result of this search. It is important to note that all 10 cases were immunocompetent patients transfused with whole fresh blood with no irradiation and no WBC reduction, nine of them in outside periphery hospitals and the tenth as an emergency life-saving procedure at our center. A couple of patients with TA-GVHD referred to our hospital were previously reported in the literature.[5,6]

Seven out of the 10 patients were males. Their ages ranged between 1 month and 67 years with the majority (6/10) being above 50 years of age. The reasons for blood transfusion included major surgeries such as coronary artery bypass graft procedures (CABG) in two of the cases, corrective procedures for hip and knee fractures and surgical exploration, excision of an infrarenal aortic aneurysm, modified radical mastectomy, and repair of femoral vessels after bullet injury. Other reasons included C-section delivery, autoimmune anemia in a newborn, bleeding, and anemia. Most of the donors were related to the patient, with the majority of blood units being donated by the son of the patient (5/10). It is interesting to note that in the emergency case, the donor was completely unrelated to the patient. The HLA types of the donor-recipient pair would have been of great value. Unfortunately, because the bulk of the transfusions were given at outside hospitals, such data is not available. Table 1 lists the general characteristics of the 10 cases in addition to the reasons for transfusion.

Upon presentation, 8 out of the 10 cases had fever above 38°C with chills, 9 had a maculopapular rash, 1 had diffuse bullae and desquamation of the skin, 6 had abdominal pain and diarrhea, 3 had nausea and vomiting, 4 had severe cough, and 1 had icteric sclera. Laboratory studies showed that all patients had severe pancytopenia with Hb levels ranging between 7.1 and 10 g per dL, WBC counts ranging between 0.1×10^9 and 0.9×10^9 per L, and platelet count ranging between 9×10^9 and 120×10^9 per L. Furthermore, all patients had elevated liver enzymes with ALT ranging between 116 and 2933 IU per L. Eight out of the 10 patients had hyperbilirubinemia with the highest value of total bilirubin being 20.6 mg per dL and that of direct bilirubin 15.6 mg per dL. Creatinine levels were normal in all patients except one, where the level was found to be 1.8 mg per dL. All patients underwent a skin biopsy and a marrow aspirate. The results of the skin biopsy confirmed the impression of TA-GVHD. Indeed, all 10 patients were found to have focal parakeratosis, extensive satellite cell dyskeratinization, and basal vacuolar degeneration. The biopsy also showed sparse-to-mild mixed inflammatory cell infiltrates around the superficial vascular plexus composed of lymphocytes and macrophages as well as nucleated debris. Marrow aspirates showed severe marrow aplasia in all 10 cases. Table 2 summarizes the laboratory results of our patients.

TABLE 1. General characteristics of the 10 cases (1991-2001)

	Age	Sex	Reason for transfusion	Units	Donors
Patient 1	67 years	M	CABG	7	Sons
Patient 2	22 years	F	C-section	1	Sister
Patient 3	1 month	M	Autoimmune hemolytic anemia	3	Cousin
Patient 4	30 years	M	Exploration and correction of femoral vessels after bullet injury	4	Cousins
Patient 5	65 years	M	Excision of infrarenal aortic aneurysm (life-saving transfusion)	5	Unrelated
Patient 6	64 years	M	CABG	2	Son
Patient 7	25 years	F	Anemia	2	Cousin
Patient 8	51 years	M	Bleeding secondary to trauma		Son and daughter
Patient 9	57 years	F	Modified radical mastectomy	2	Son
Patient 10	60 years	M	Correction of right hip and knee fracture	8	Sons and daughters

TABLE 2. Laboratory results at the time of diagnosis of the 10 cases (1991-2001)

	Hb (g/dL)	Hct (%)	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	Bilirubin (T/D)* (mg/dL)	ALT (IU/L)	Alkaline phosphatase (IU/L)	Creatinine (mg/dL)
Patient 1	9.6	30	0.5	9	0.4/0.2	116	186	1.8
Patient 2	8.6	26	0.3	18	20.6/15.6	655	592	0.7
Patient 3	7.1	21	0.6	57	3/1.2	456	179	0.3
Patient 4	10.0	30	0.8	120	10.2/9.3	2933	1100	1.1
Patient 5	10.0	30	0.6	96	8.6/7.0	148	252	1.3
Patient 6	10.0	30	0.2	9	7.4/5.2	222	86	1.0
Patient 7	7.7	23	0.8	36	5.5/3.2	169	176	1.0
Patient 8	9.6	28	0.7	55	4.1/1.5	128	301	1.2
Patient 9	9.0	27	0.1	5	14.1/11.5	132	350	1.3
Patient 10	9.9	28	0.9	85	8.4/7.4	381	324	0.7
Normal values	12-18	37-54	4-11	250-450	0-1.2/0-0.3	0-50	35-120	0.6-1.4

* T/D = total/direct.

TABLE 3. Treatment regimen and survival duration in the 10 cases (1991-2001)

	Steroids (1 mg/kg/day)	Cyclosporine (5 mg/kg/day)	G-CSF (5-10 mg/kg/day)	Antilymphocyte globulin (5 mg/kg/day)	OKT3 (5 mg/day)	Survival duration (days)
Patient 1	+	–	–	–	–	27
Patient 2	+	+	–	–	+	6
Patient 3	+	–	–	–	–	50
Patient 4	+	–	+	–	–	3
Patient 5	+	–	+	–	–	10
Patient 6	+	–	+	+	–	8
Patient 7	+	–	+	+	–	14
Patient 8	+	+	+	+	–	60
Patient 9	+	+	+	+	–	20
Patient 10	+	+	+	+	–	7

Several modalities of treatment were used over the years according to the recommendations at the time. Two out of the 10 patients received steroids only. Two received steroids and G-CSF, and another one received steroids, cyclosporine, and OKT3. Two patients were treated with a combination of steroids, G-CSF, and antilymphocyte globulin. The remaining three received the same regimen in addition to cyclosporine. The disease was fatal in all 10 cases with respiratory failure following a pneumonia being the direct cause of death in most cases (9/10). The mean duration of survival ranged from 3 days to 2 months (mean, 20 days). Table 3 summarizes the treatment regimen and the survival duration of these cases.

DISCUSSION

TA-GVHD rarely occurs, although the precise incidence of this transfusion-induced disease is clearly unknown and most likely much higher than what is generally assumed because of under-recognition and under-reporting. In fact, the clinical presentation of TA-GVHD is so similar to other conditions (e.g., infections, drug eruptions) that the diagnosis can be easily missed.

Several risk factors for the development of TA-GVHD have been defined.[3] Although TA-GVHD was first recognized in immunosuppressed patients, there is growing awareness of its occurrence in immunocompetent patients, with several reports being published in the literature.[2,7]

TA-GVHD is almost impossible to treat effectively despite the presence of some reports in the literature about resolution of the disease with cyclosporine and anti-CD3 MoAb (OKT3) and with antithymocyte globulin and steroids.[8,9]

Because the mechanism of the disease involves the activation of donor lymphocytes against recipient HLA antigens, the prevention of TA-GVHD relies on the removal of WBCs contained in donor products or on their deactivation. Studies have shown that the activity of lymphocytes declines with the length of storage of the blood, which implies that the risk of activation of these lymphocytes against the recipient cells is higher when fresh blood is used for transfusion. Although lymphocyte viability in vivo may persist up to 10 to 14 days, the ability to cause this complication greatly decreases after 48 hours. This is why the use of stored units is preferred.[10]

One effective way of inhibiting donor lymphocytes and preventing their proliferation is by irradiating the blood units before transfusing them. An appropriate irradiation dose must be used. The FDA recommends the dose of 2500 cGy for the irradiation of blood elements,[11] although it has been proven that other blood components such as RBCs, platelets, and granulocytes are not significantly affected if doses up to 5000 cGy are used.[12] The AABB, however, recommends not storing the irradiated RBCs for more than 28 days after irradiation.[11]

However, not every unit of blood to be transfused should be irradiated first. In fact, there are several indications for the irradiation of blood elements and these are evolving as more and more concern is being directed toward the problem caused by TA-GVHD. An important fact to note is that these recommendations are different in different parts of the world. For example, in the United States, the AABB requires the irradiation of blood products in cases of intrauterine transfusions and blood units donated by family members or by HLA-matched individuals and when the patients are at risk for TA-GVHD, especially organ transplant recipients, patients with hematologic disorders who will be undergoing allogeneic and autologous HPC transplantation, patients with congenital cellular immunodeficiency, and patients with Hodgkin's disease. On the other hand, in Japan where the incidence of TA-GVHD seems to be the highest,[3] the recommendations for blood irradiation are very strict and much broader. For example, all patients undergoing cardiovascular surgery should receive irradiated blood, which is not the case in the United States and Europe. Other indications for irradiation in Japan include surgical operations for malignancies, congenital immunodeficiencies, HPC transplantation, and premature babies.[13] Therefore, in populations that have more homogeneity in HLA types, broader indications may be reasonable.

WBC reduction has been proven not to be effective when used alone in preventing the development of TA-GVHD. Indeed, there are several reports in the literature about patients who developed TA-GVHD after WBC reduction by filtration.[14,15] However, the use of this preventive method in combination with irradiation of blood units may provide the patients with additional protection. Furthermore, newer filters are being developed and should theoretically be more effective, but their ability to interdict this complication is currently unknown.

The 10 patients we are presenting in this paper were all immunocompetent. Nine of them received fresh (<3 days of storage) blood transfusions at outside peripheral hospitals that do not follow strict preset guidelines for blood transfusion. The number of units transfused in these institutions overall in the time period we are considering is unfortunately not available to us in order to generate denominator data and put the risk into perspective. The 10th (Patient 5) received whole blood from an unrelated donor as an emergency life-saving procedure at our center. None of the units were irradiated nor leukoreduced. The mortality rate was 100 percent. None of the surgical procedures or medical diseases of these 10 patients are listed by the AABB as prerequisites for irradiation of blood units before transfusion. However, the main issue is that in 9 out of the 10 cases, the blood was donated by family members, and this fact by itself is alarming. Indeed, the AABB recommends that any blood unit donated by a family member should be irradiated before transfusion, which was not the case in the hospitals where the transfusion was given. Furthermore, the rate of consanguineous marriages in the Lebanese population is relatively high when compared to the American and European communities, which would definitely increase rates of HLA homozygous individuals and thus donor in the population. Another problem faced in our country is the absence of a central blood bank, which would keep track of all blood units and manage all transfusions according to strict and unified guidelines, unlike the present situation where every hospital probably follows its own recommendations. The incidence of TA-GVHD is definitely underestimated in our country because AUBMC is a tertiary referral care center. We assume that many cases must have occurred in smaller hospitals without being referred to us and that several of these may have been misdiagnosed as viral infections and other diseases with a similar presentation.

In view of all the above-mentioned facts, a very important question raises itself. What can be done in Lebanon to prevent the occurrence of TA-GVHD? It seems that the most important plan to follow relies on the adoption of unified guidelines for transfusion and irradiation of blood products in all the hospitals with the creation of a central blood bank. Transfusions from close relatives should be avoided as much as possible. This may be achieved by the creation of a solid voluntary blood-donor system. Furthermore, taking into consideration the case of Patient 5 and keeping in mind the high rate of consanguinity in our country, should we irradiate all blood units given as an emergency life-saving procedure? We also highly recommend reporting all cases of TA-GVHD in Lebanon as to have a single registry for all these patients. Moreover, the physician's index of suspicion should be very high when patients who recently received blood transfusions present to them with symptoms that may hint to TA-GVHD. Such patients should directly be referred to a tertiary care center where they can be taken care of in a better setting.

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