Transfusion-Associated Graft-versus-Host Disease

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Received April 12, 1990

The clinical pathologic syndrome of graft-versus-host disease (GVHD) is usually a sequela of bone marrow transplantation. This disorder occurs as a result of recognition by engrafted donor-derived lymphocytes of "foreign" recipient transplantation antigens. GVHD may also result from engraftment of lymphocytes from other sources, including (1) transfusion of lymphocytes containing blood components, (2) transplacental maternal fetal transfusion, and (3) passive transfer of lymphocytes in solid organ transplantation. The recipients are usually severely immunodeficient and thus incapable of rejecting the transfused lymphocytes. This syndrome may, however, also develop in immunologically competent patients receiving blood products from individuals with histocompatibility antigens not recognized as foreign.

GRAFT-VERSUS-HOST DISEASE: CLINICAL SYNDROME

Graft-versus-host disease (GVHD) is a clinico-pathologic process which develops predominantly in the setting of bone marrow transplantation. It is, in fact, the major rate-limiting step in the utilization of marrow grafting for the treatment of a host of human diseases, often presenting with life-threatening complications even in recipients of histocompatible transplants. An extremely high incidence of severe GVHD is noted in the setting of bone marrow transplants from non-histocompatible marrow donors. Thus, the absence of an appropriate HLA-(histocompatible locus antigen) compatible, MLC (mixed lymphocyte culture) non-reactive donor may prevent the use of this therapeutic modality in patients for whom it represents pathophysiologically rational treatment. A variety of pharmacologic and biologic therapies have been tried for the purpose of ameliorating or eliminating this condition. Based on the fact that T cells appear at least to initiate this condition, ex vivo depletion of T lymphocytes from the bone marrow has been attempted to overcome these barriers.

Clinically, graft-versus-host disease in the setting of marrow transplantation may manifest itself as two distinct syndromes. The first is an acute syndrome, appearing from seven to 50 days post-transplant, and is associated predominantly with a skin eruption, hepatitis, and gastrointestinal dysfunction [1]. The dermatologic manifestations may vary from a mild diffuse erythematous rash to a severe epidermal necrolysis syndrome. The hepatic syndrome is predominantly reflected by hepatocellular enzyme and bilirubin abnormalities, and the gastrointestinal dysfunction is associated with nausea, vomiting, and diarrhea. Characteristic pathologic findings are noted, particularly in the skin [2,3]. Acute GVHD may occur in 40–80 percent of patients who receive histocompatible transplants, with a severe syndrome developing in 30 to 50 percent of recipients despite treatment with a variety of GVHD prophylaxis regimens.

Abbreviations: GVHD: graft-versus-host disease  HLA: histocompatible locus antigen  MLC: mixed lymphocyte culture

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Treatment of moderate to severe acute GVHD includes the use of high-dose pulse corticosteroids, antithymocyte serum, cyclosporine, and a variety of monoclonal antibody preparations. These therapeutic modalities result in resolution of the acute syndrome in approximately 50 percent of patients [7]. The second syndrome, chronic GVHD, may develop from two months to one year post-transplant and has distinctive clinical and pathological manifestations [8]. This reaction also predominantly affects the skin, liver, and gastrointestinal tract and has many of the characteristics of scleroderma. Bone marrow transplant recipients with histocompatible donors may develop one or both of these reactions.

From a pathophysiological point of view, graft-versus-host disease results from engrafted donor lymphocytes which recognize a foreign antigen in the recipient [9]. In the case of histocompatible donors, the lymphoid cells presumably recognize a minor non-HLA antigen. Extensive animal studies have demonstrated that the more disparate the donor and recipient, the more frequent and severe the reaction [10]. Second, although the pathophysiology of the entire cascade of events in the graft-versus-host disease reaction is unclear, the event is initiated by a T lymphocyte. The severity of the reaction has been demonstrated in part to be dependent upon the number of T lymphocytes contaminating the bone marrow infusion [10]. Thus, both the degree of disparity and the number of engrafted lymphocytes influence the incidence and severity of the GVHD reaction. Of interest is the fact that an acute GVHD-like syndrome has been noted in some recipients of syngeneic (identical twin) or autologous (self) transplants, in which neither major histocompatibility nor presumptive minor histocompatibility antigenic differences would be expected [11]. This observation suggests that other processes, possibly of an "autoimmune" nature, result in this reaction in some situations.

**TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE**

Although graft-versus-host disease is primarily associated with bone marrow transplantation, this reaction has also been noted on occasion in other settings. In particular, GVHD has resulted from blood transfusions with a variety of products, transplacental transfusions, or passive administration of lymphocytes in solid organ transplants. Again, the requirements for GVHD in these settings include: (1) engraftment of viable donor T lymphocytes capable of further cell division, (2) the recognition of foreign transplantation antigens by the donor lymphocytes, and (3) failure of the host recipient's immune system to eliminate or reject the donor T cells. This last requirement is what prevents routine blood transfusion from establishing GVHD in recipients more frequently. The majority of transfusion recipients are sufficiently immunocompetent, in particular have an adequate T-cell response, to reject the donor T lymphocytes before the latter can establish GVHD.

The overall risk of transfusion-associated GVHD is unknown and is probably higher than the approximately 60–70 cases reported in the literature [12,13]. In fact, many tertiary institutions, where patients at high risk are routinely treated, establish a diagnosis of transfusion-associated GVHD approximately once a year. Transfusion-associated GVHD is probably often unrecognized in the setting of complex medical situations, where target organs are already dysfunctional. Furthermore, incomplete manifestations of the triad of GVHD may be present, or the syndrome may be mild. Finally, the potential diagnosis may be missed and not associated with a transfusion administered up to a month previously.
Since transfusion-associated GVHD is preventable, the question of who is at risk must be addressed. Clearly the cases presented in the literature establish certain high-risk populations of patients. These groups include children with the relatively rare genetic immunodeficiency states, including severe combined immunodeficiency, DiGeorge syndrome, and the Wiskott-Aldrich syndrome [14-17]. Since the T-cell compartment is usually intact in either the acquired or congenital hypogammaglobulinemias, GVHD has not been reported in this setting. A second group at high risk are neonates, particularly those who have received either intrauterine or postnatal exchange transfusions [18]. In this setting, the immune system of the newborn may be insufficiently mature to reject transfused foreign T cells. Furthermore, massive transfusions may result in either immunological tolerance or further immune suppression [19]. Finally, a group at high risk for GVHD are all allogeneic or autologous bone marrow transplant recipients. This risk results from the chemoradiation preparative regimens, which render the patient totally immunodeficient, as well as the prolonged immunologic recapitulation post-transplant [20,21]. Patients are treated as susceptible to transfusional GVHD for their entire lives, although this susceptibility has never actually been tested. The incidence of reported transfusion-associated GVHD post-marow grafting is low, because it has long been established practice to administer only irradiated blood products to these patients. Furthermore the situation is further confused by the fact that the development of GVHD is most commonly associated with the donor lymphocytes in the transplant. In one series of autologous bone marrow transplants, however, four of 25 patients receiving unirradiated blood products developed fatal GVHD [22].

Groups at lower, but some, risk include patients receiving chemoradiation therapy for malignancies, which results in marked immunosuppression. Thirty cases have been reported, predominantly in patients with hematologic malignancies, including 11 patients with Hodgkin's disease, five patients with non-Hodgkin's lymphoma, nine with acute non-lymphocytic leukemia, and five with acute lymphoblastic leukemia [12,13]. Only four cases have been reported in association with treatment for solid tumors [23-26]. The risk of post-transfusion-associated GVHD in this setting is very difficult to establish and is clearly variable, depending upon the treatment regimen. In addition, mild cases are probably underdiagnosed in this setting, and the incidence is probably higher than reported. Given the few cases reported in these more common disorders, however, a definite but lower risk must be assumed. Of note is that over two-thirds of the patients had malignancies of the lymphoid system. Perhaps a disease-associated immune defect exists and/or the therapy for these diseases is more immunosuppressive. In most cases in which transfusion-associated GVHD is noted, the patients have received extraordinarily intensive therapy, and GVHD occurs during the period of intense immunosuppression.

Of note is the fact that to date no cases of transfusion-associated GVHD have been reported in patients with the acquired immunodeficiency state, despite a profound T-cell defect as well as frequent transfusion therapy. Perhaps transfused lymphocytes are immunologically immobilized by the same retroviral infection. Similarly, only a rare case of GVHD has been noted in recipients of solid organ transplants, despite massive transfusions and prolonged and intense immunosuppression [27,28]. The GVHD which occurs in this setting could result from either blood transfusions or passive transfer of lymphocytes in the donor organ. The author has noted prolonged engraftment of Philadelphia chromosome positive donor cells for six months in a renal
transplant recipient who received an unirradiated granulocyte transfusion from a patient with chronic myelogenous leukemia [unpublished observation]. In at least two-thirds of patients with acquired aplastic anemia, an intact immune system can be demonstrated, and thus only one case of transfusional GVHD has been observed in a patient with severe aplastic anemia [29]. Theoretically patients with severe aplastic anemia undergoing immunosuppressive therapy with antithymocyte globulin, cyclosporine, or high-dose corticosteroids should be at risk for transfusion-associated GVHD, but no cases have yet been reported, despite the fact that these patients do not consistently receive irradiated blood. Perhaps in this setting the multiplicity of transfusions results in a graft-versus-graft reaction, with destruction of potential lymphoid engraftment of any given donor.

POST-OPERATIVE ERYTHRODERMA

In the mid 1950s, several cases of post-operative erythroderma were reported in presumably immunologically normal Japanese recipients of blood transfusions [30]. Most of these transfusions were relatively fresh units of whole blood donated by family members. Only years later was the fact recognized that this reaction did not represent a drug allergy, but was post-transfusion graft-versus-host disease. A number of cases, 90 from Japan, have been documented more recently in immunologically normal individuals [31]. The issue became clearer with the report from Israel of two cases of fatal post-cardiac surgery transfusion-associated GVHD [32]. In both cases, unirradiated blood transfusions from children of the patients were administered. HLA typing of the respective donors demonstrated that the donors were HLA-homozygous and thus did not have HLA-A or HLA-B antigens that were foreign to the recipient. This circumstance, in which fresh blood with large numbers of viable lymphocytes was administered, allowed engraftment of immunocompetent donor lymphocytes, which then recognized the recipient as foreign, provoking a subsequent GVHD reaction. In one Japanese case, similar findings were noted [33]. The Japanese have recently reported an incidence of fatal transfusion-associated GVHD in 0.2 percent of patients undergoing cardiac surgery [34]. This reaction may in part be due to the use of large amounts of relatively fresh blood but has probably been largely noted in Japan because of the practice of utilizing family members as blood donors, as well as the fact that a relatively limited HLA gene pool exists in this genetically homogeneous population. Clearly, as blood transfusion practices change in response to fears of transfusion-transmitted infections, caution will have to be exercised in the use of directed donations from family members. Certainly fresh blood products should be avoided, if possible.

NON-TRANSFUSION, NON-BONE MARROW TRANSPLANT GVHD

Other sources of non-bone marrow transplantation GVHD have also been reported. Clearly, passive transfer of lymphocytes in solid organ transplants into immunosuppressed recipients is a possible cause [27,28]. Relatively small numbers of lymphocytes are present in the vasculature of the kidney, heart, liver, and lung, and the number is probably further diminished by flushing with the organ preservatives; however, large numbers of lymphocytes are transplanted in recipients of spleen, pancreas, or gastrointestinal transplants. In order to prevent GVHD, low-dose irradiation is often administered to these organs ex vivo. Another documented source of GVHD is the placental transfer of maternal T cells to fetuses with severe combined immunodeficiency, with subsequent engraftment. In three cases, GVHD was ascribed to this phenomenon by
tying of the lymphocytes [35–37]. A subsequent sequential study in these children demonstrated, however, that, despite a 25 percent incidence of engraftment, the maternal-fetal GVHD syndrome was rarely observed [38]. In vitro functional studies of the transplanted maternal lymphocytes demonstrated that they were immunoincompetent.

LYMPHOCYTE SOURCES

The risk of graft-versus-host disease has been demonstrated to be dependent upon the dose of administered lymphocytes in both mice and humans. As few as \(10^7\) lymphocytes/kg or perhaps less can cause fatal GVHD; hence sufficient lymphocytes can be transfused from a single unit of blood, which contains from 1 to \(2 \times 10^9\) lymphocytes [39]. Viable lymphocytes have been detected in two- to three-week-old blood, although most reported cases have resulted from relatively fresh packed cells or whole blood. GVHD has also been observed following the transfusion ofuffy coats, platelets, and granulocytes, indicating that sufficient lymphocytes exist in these preparations to induce the reaction. Fresh plasma, with relatively fewer lymphocytes (\(1.5 \times 10^5\) lymphocytes) has only been implicated as the source of transfusion-associated GVHD in small children with congenital severe immunodeficiencies [40]. No reports have implicated fresh frozen plasma or cryoprecipitate. The lower limit of requisite numbers of lymphocytes is unclear; however, the dose dependency may make children more susceptible than larger adults.

CLINICAL SYNDROME, DIAGNOSIS, AND TREATMENT OF TRANSFUSION-ASSOCIATED GVHD

The clinical syndrome is similar in many respects to that associated with post-bone marrow transplant GVHD. Fever is commonly the presenting symptom, occurring four to 30 days, with a median of eight days, following the transfusion. A skin rash develops either simultaneously or shortly thereafter and may vary in intensity from diffuse erythema to a maculopapular eruption to a toxic epidermal lysis picture. Liver dysfunction is primarily hepatocellular, and the syndrome is often accompanied by watery diarrhea. All three organs have characteristic histological manifestations described extensively elsewhere [1]. A unique aspect of post-transfusion GVHD is an associated pancytopenia with bone marrow aplasia in 66 percent of patients [41]. This distinguishing aspect differs from bone marrow transplant GVHD since, in the latter situation, both the lymphoid system and hematopoietic cells are derived from the donor. One case has been reported in which transfusion GVHD resulted in rejection of a bone marrow graft [42]. Unlike bone marrow transplant-related GVHD, the majority of reported cases following transfusion have been fatal, with infection as the primary cause of death. The poorer survival may be due to the greater genetic disparity encountered in the post-transfusion state. A somewhat better survival has been noted in patients treated for acute non-lymphocytic leukemia. Only rarely has chronic graft-versus-host disease been reported post-transfusion [43].

The diagnosis of GVHD is usually established by the clinical features as well as classic histopathology. A number of viral infections, particularly cytomegalovirus, can mimic this syndrome and are common in similar clinical scenarios. Reactions to a variety of drugs, including chemotherapy and antibiotics, must also be considered. Irradiation therapy can also cause similar findings. Of interest is the development of autologous or syngeneic graft-versus-host disease with reconstitution of an unbalanced
immune system [11]. A rat model has demonstrated a cyclosporine-associated GVHD reaction [44]. Thus, autologous GVHD must be considered, but this reaction is usually a mild syndrome. The diagnosis of transfusion-associated GVHD can be strongly supported by evidence of lymphoid engraftment. This process can be demonstrated through cytogenetic studies and/or through HLA typing of lymphocytes. Both of these studies can be difficult because of the usual lymphopenia. HLA typing may demonstrate a number of findings, including the identification of more than two HLA haplotypes or, in the case of homozygous donors, only a single haplotype. Family studies may need to be done to confirm the patient's genotype. Retrospective HLA typing of the blood donors can confirm the source of the GVHD.

Treatment of post-transfusion GVHD has in general been unsuccessful. Patients have been treated with high-dose corticosteroids, antithymocyte globulin, monoclonal antibodies, and cyclosporine. Despite therapy, mortality rates of 80–90 percent have been noted, with the best survival in patients being treated for acute non-lymphocytic leukemia. Presumably, in the latter situation, ultimate recovery of the patient's own immune system results in rejection of the engrafted lymphocytes. A better survival has also been noted in recipients of granulocytes from donors with chronic myelogenous leukemia [45].

**PREVENTION**

Since treatment of transfusion-associated GVHD has been unsuccessful, the main effort should be prophylaxis. Techniques to remove leukocytes physically from blood products may reduce the number of viable lymphocytes by 1 to 3 logs but will not entirely eliminate the putative effector cells [46,47]. These techniques include washing or freezing red cells in glycerol or DMSO, or filtration of platelets. As many as 10⁶ lymphocytes, perhaps a number adequate to produce GVHD in severely immunosuppressed children, may be found in a filtered transfusion.

At the present time, prophylactic *ex vivo* irradiation of blood products prior to transfusions is the most efficient and standard method for GVHD prevention. In most centers, irradiation is administered in a few minutes, with relatively cheap and compact cesium 137 sources with a rotating chamber adequate to hold a unit of blood. Blood bank technologists can quickly master the technique. Attention does need to be paid to quality control. For centers with less frequent needs for irradiated blood products, conventional X-ray therapy equipment can be utilized, but this method is a cumbersome process, requiring a number of individuals. Although the current doses administered are usually between 1,500 and 3,000 rads, debate still exists about the appropriate dose. Clearly, doses of 1,500 rads will decrease the response of lymphocytes to mitogens by 85 percent and will prevent a response in a mixed lymphocyte culture [48,49]. The latter reaction is the *in vitro* correlate of the *in vivo* graft-versus-host reaction. Of concern is one recent report in which both graft rejection and graft-versus-host disease was provoked by blood previously irradiated with 1,500 rads, suggesting that the lower limit should be raised to 2,000 rads [42]. This change might be seriously considered for situations in which HLA-identical blood products are being administered to severely immunosuppressed individuals such as bone marrow transplant recipients.

Clearly, since increasing the dose incurs minimal time and virtually no expense, the major limitation would be a deleterious effect on the desired transfusion product. Mature erythrocytes appear to be resistant to large doses of irradiation with normal red
cell survivals and function, even if the cells are irradiated after prolonged storage [49]. Prolonged storage after irradiation does result in an increased plasma hemoglobin and potassium, and a slight increase in red cell adenosine triphosphate and 2,3-diphosphoglycerate concentrations [49,50]. Thus, red cells should not be stored for prolonged periods after irradiation. Platelets also seem to be relatively radiation-resistant, with a normal chromium survival at the usually administered doses, although one study suggests a diminished initial recovery and diminished correction of the aspirin defect [49,51,52]. Unlike red cells, five-day storage of irradiated platelets does not seem to have an adverse effect [53]. The results in granulocyte transfusions seem to be more variable, with the suggestion that, at the higher ranges of conventional irradiation doses, some loss of function may be incurred [49,54–56]. It must be remembered, however, that granulocyte transfusions may be the blood product most heavily contaminated with lymphocytes. Whether or not these ex vivo defects are correctable in vivo is unclear. Two theoretical adverse effects need to be considered. The first is that irradiation might promote increased leaching of plasticizer into the blood product [49]; to date, no such effect has been noted. Second, although circulating pleuripotential stem cells are extraordinarily sensitive to irradiation and are most likely destroyed by the irradiation, a chromosomally damaged, but otherwise intact cell could engraft, with the subsequent development of a hematopoietic malignancy.

More recently, ultraviolet irradiation has been studied in the prevention of alloimmunization by transfusion products [57]. One study demonstrated the abrogation of transfusion-induced GVHD in dogs [58]. This technique is under further investigation, including methods for the uniform administration of the ultraviolet light. The mechanism is unclear but currently is thought to affect both DNA and cell membranes. Adverse effects have yet to be fully investigated.

SUMMARY

In summary, fatal graft-versus-host disease can be induced when blood products containing viable lymphocytes are administered to and subsequently engraft in severely immunosuppressed recipients. Many appropriate clinical scenarios have been described, although this syndrome is probably underdiagnosed and underreported. As more aggressive therapeutic modalities are developed, the potential for the development of this syndrome in treated patients must be carefully considered. Furthermore, recent descriptions of otherwise immunologically normal patients developing this syndrome have been noted. In the latter situation, large numbers of lymphocytes expressing HLA antigens that are not recognized as foreign by the recipient engraft in the host and recognize foreign host antigens, initiating the GVHD reaction. The routine use of family-related transfusions should be carefully reconsidered and reserved for special circumstances. Alternatively, a policy of irradiation of directed donations can be considered. Since treatment of transfusion-associated GVHD syndrome has been unsuccessful, appropriate prophylaxis with ex vivo irradiation of blood products will successfully prevent the development of this transfusion complication in susceptible recipients.

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