The hyperimmunized patient: from sensitization toward transplantation

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Abstract. Hyperimmunized patients tend to accumulate on renal transplant waiting lists because their high level of sensitization leads to positive crossmatches with almost all potential organ donors. The origins of sensitization and the different efforts made to find crossmatch-negative donors for these patients are discussed. Special emphasis is given to a local strategy based on the determination of HLA-A and -B mismatches, against which the patient did not form alloantibodies, the so-called acceptable mismatches. Kidney donor selection is based on compatibility with the patients' own HLA antigens in combination with the acceptable HLA-A and -B antigens and can be operated from a central organ-sharing office.

Key words: Hyperimmunized patient - HLA - Sensitization - Acceptable mismatch - Transplantation.

The accumulation of highly sensitized patients on renal transplant waiting lists is a universal problem. Because these patients have alloantibodies against many HLA alloantigens, it is very difficult to find a crossmatch-negative graft for them. For that reason, the average waiting time is much longer for these patients than for patients with fewer or no alloantibodies [12].

Furthermore, the transplantation results in the group of highly immunized patients are generally less successful [16], resulting in a relatively high number of highly sensitized patients returning to the waiting list for retransplantation.

In this paper we deal with three topics:

1. Why do patients become highly sensitized?
2. Which schemes are developed to increase the chance of finding a donor for highly immunized patients?
3. A special strategy developed in our center to predict and select crossmatch-negative donors for highly sensitized patients is described.

Origins of sensitization

In contrast to sensitization against the AB0 blood groups, natural antibodies do not play a role in sensitization against the HLA alloantigens. Therefore, patients with alloantibodies should have had contact with foreign HLA antigens in one way or another. The three main reasons for sensitization in patients waiting for a renal allograft are pregnancy, blood transfusion, and failed transplants [12]. It is therefore not surprising that females are predominant among the (highly) sensitized patients.

However, this higher incidence of sensitization is not only due to antibody formation against the paternal HLA antigens of the fetus during pregnancy. Several reports have suggested that multiparous women are more likely to develop broadly reactive antibodies after blood transfusions [17, 22]. Patients who are homozygous for one of the supertypic HLA antigens, i.e., Bw4 and Bw6, are also at risk of developing broadly reactive antibodies after one or a few blood transfusions, as are patients who have rejected a previous graft, especially when the rejected graft carried several HLA-A and -B mismatches [14].

Although the three risk factors (pregnancy, transfusion, and graft rejection) can easily be
determined, not every patient has the same chance of becoming sensitized after such contacts with HLA alloantigens [20]. The reason for that may be either the immunogenicity of the product used as a challenge or immune response genes in the patient that predispose to antibody formation against foreign HLA antigens. Several factors may contribute to the immunogenicity of the blood used for transfusions, such as the amount of blood given per transfusion or the number of transfusions. A very important factor is the amount of viable leukocytes in the transfusate. Systematic studies on the immunogenicity of platelets both in man [7] and in the mouse [4] have shown that the presence of viable leukocytes in the platelet suspension is a prerequisite for the induction of alloantibodies against the MHC antigens. The presence of foreign MHC class II antigens is probably necessary for the activation of T-helper cells in the recipient, which in turn will activate B-cells to develop into alloantibody-producing plasma cells. Also, others have found that the probability of sensitization in renal transplant patients increases with an increasing number of viable leukocytes in the transfused blood [15]. Of course, the number of HLA mismatches between donor and recipient plays a determining role as to whether a patient will become sensitized after an immunizing event such as blood transfusion or transplantation. However, even when challenged with several very immunogenic products, only a minority of the patients become highly sensitized.

For instance, HLA-DRw6-positive patients are more likely to reject an HLA-DR-mismatched graft [10] and to develop antibodies reactive with B-cells and monocytes after transplant rejection than are patients with other HLA-DR antigens [11]. On the other hand, the HLA-DR1 antigen has been associated with low sensitization and a high kidney transplant survival [6]. A third example is the HLA-DR2 antigen, which seems to be associated with a high level of sensitization after blood transfusion, especially in females with previous pregnancies (A.Brand, personal communication). These data suggest that genetic factors in the recipient also play a role in the level of sensitization against HLA alloantigens. As these patients have an increased or decreased reactivity against many different alloantigens, it remains to be established whether these phenomena can be explained by mechanisms similar to those involved in the function of immune response (Ir) genes that control antigen-specific immune responses.

In conclusion, the main risk factors for a patient's becoming highly sensitized are pregnancy, blood transfusion, and graft rejection. However, both the immunogenicity of these allogeneic factors and genetic factors in the recipient will determine whether a certain patient will actually become a highly immunized patient, for whom it is very difficult to find a suitable donor.

Schemes to increase the chance of finding a kidney donor for highly immunized patients

Highly immunized patients have antibodies against almost all foreign HLA antigens and are very difficult to transplant because the crossmatches with almost all donors are positive. When these patients are treated like all other patients in terms of donor selection and urgency, they accumulate on the renal transplant waiting lists. Therefore, several strategies have been developed to increase the chance of finding a crossmatch-negative donor for them. One possibility is to select HLA-A and -B identical or compatible donors, but the chance of finding such a donor is often very low due to the enormous polymorphism of the HLA system. Other schemes involve the distribution of the sera from these patients to many tissue-typing laboratories. Each potential donor is tested against these sera, and by trial and error donor-recipient combinations with negative crossmatches are identified [1, 21]. HLA matching is hardly or not at all involved in these schemes, although several reports have suggested that matching the donor and recipient for the HLA-DR antigens will significantly improve graft survival [12, 13]. These schemes have contributed to a shorter waiting time for highly immunized patients, although transplantation results could be further improved with DR matching.

Other approaches have also been suggested to solve the problem of highly sensitized patients, who have so many different antibodies in their serum that all crossmatches with HLA-mismatched donors are positive. For instance, the removal of preformed alloantibodies by cyclophosphamide treatment in combination with plasma exchange has been reported to be helpful in some highly sensitized patients [24]. However, this treatment is rather aggressive, often resulting in infectious complications and even death in some patients [9].

A new approach has recently been described for the removal of alloantibodies from the serum of highly immunized patients by the extracorporal immunoadsorption of the anti-HLA antibodies by staphylococcous protein A columns [18]. Although up to now only two patients have been successfully transplanted, with a positive crossmatch with serum