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A Review of Humoral Rejection in ABO-Incompatible Kidney Transplantation, with Local (Intrarenal) DIC as the Underlying Condition

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Summary. **The underlying condition associated with humoral rejection in ABO-incompatible kidney transplantation is local (intrarenal) disseminated intravascular coagulation (DIC). Anti-A and anti-B antibodies adhere to blood group antigens on vascular endothelial cells, triggering antigen-antibody reactions, which cause endothelial cell injury. This, in its turn, induces the production of cytokines, migration factors, and free radicals, which activate platelets and complements, and induce thrombi, the migration of granulocytes and macrophages, and phagocytosis. As lesions progress, interstitial hemorrhage as well as necrosis and infarction due to ischemia are also caused. The degree of renal dysfunction is determined by the amount of antibodies (antibody titer), the degree of vascular endothelial injury, and the site of the lesions in blood vessels (arteries). (Fig. 1).**

Key words—ABO-incompatible kidney transplantation, anti-A and anti-B antibodies, humoral rejection, hyperacute rejection, local DIC, intrarenal DIC, Banff classification.

Introduction

In Japan, cases of kidney transplantation remain rarer than in the US and Europe due to an extremely small number of cadaveric kidneys.[1,2] In order to cope with this situation, ABO-incompatible kidney transplantation has been undertaken in about 300 cases since 1989.[3-15] Although generally favorable outcomes have been reported, it is not surprising that the success rate has not been as high as in matched or minor-mismatched transplantation, mainly due to humoral rejection.

In this paper, I shall demonstrate that local disseminated intravascular coagulation (DIC) is the underlying condition associated with humoral rejection based on findings obtained thus far in ABO-incompatible kidney transplantation, and discuss the classification and treatment of rejection reactions in kidney transplantation.

1. Findings obtained in ABO-incompatible kidney transplantation

Outcome

The success rate is slightly but not statistically significantly lower in ABO-incompatible transplantation than in matched or minor-mismatched transplantation.[16]

Anti-A and anti-B antibodies

1) Humoral rejection is liable to occur in recipients with high pre-transplantation antibody titer or those in whom a rebound phenomenon occurs after antibody elimination, and humoral rejection results in graft loss in severe cases.[17]

2) Antibody titer decreases to almost 0 shortly after transplantation, suggesting that antibodies are adsorbed to the kidney.

3) Bacterial infections sometimes trigger increases in antibody titer, leading to humoral rejection reaction.[18]

Rejection

1) In the past, incompatible kidney transplantation

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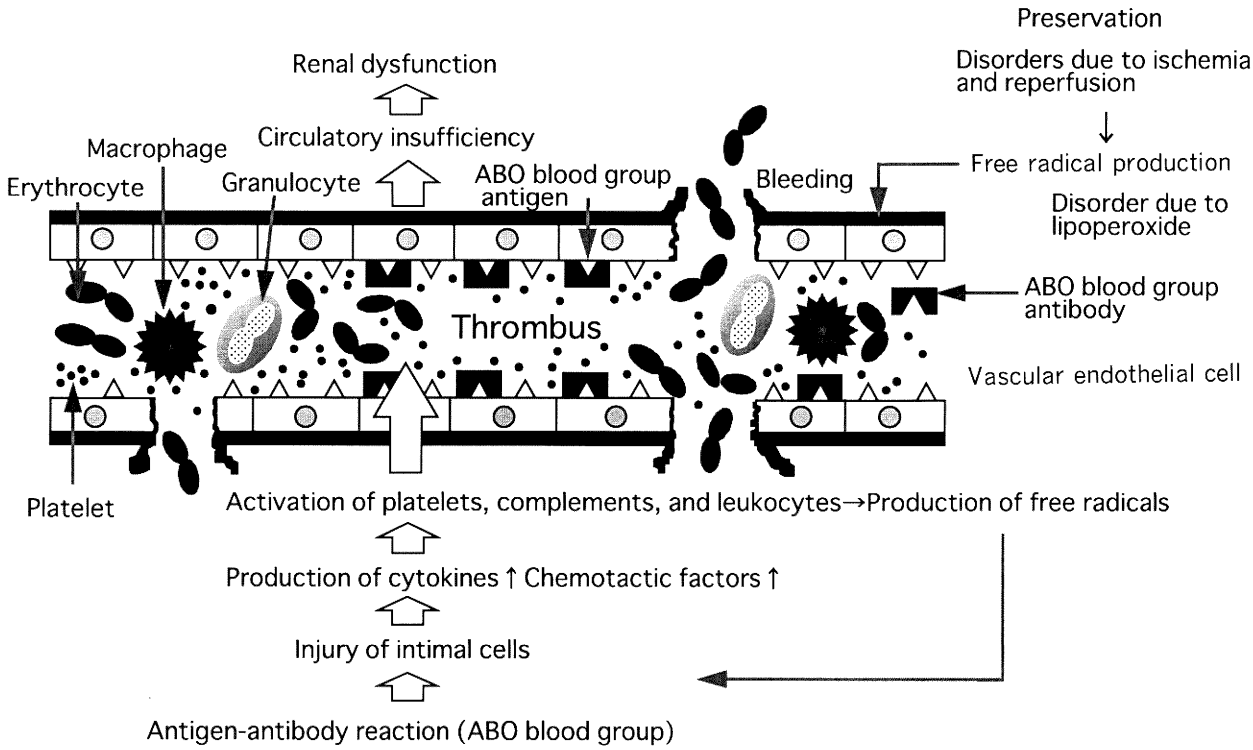


Fig. 1. Humoral rejection reaction in ABO blood group incompatible kidney transplantation (intrarenal DIC) and its mechanism.

was conducted without eliminating antibodies before transplantation. In some of these cases, hyperacute rejection occurred shortly after transplantation, leading to graft loss, a phenomenon called "white kidney" or "blue kidney".[19-21]

2) Clinical symptoms and findings associated with rejection at an early period after transplantation include transient high fever, marked decreases in platelet counts, and swelling of the graft.

3) Humoral rejection is added to cellular rejection in rejection reactions observed within 1 month after transplantation.[23,24]

4) Incidence of acute rejection attributable to humoral factors decreases several months after transplantation.

5) The degree of cellular rejection does not necessarily correlate with that of humoral rejection.

Histopathology

1) A one-hour biopsy occasionally shows thrombi, erythrocyte rouleaux formation, and granulocyte migration in Henle's loops and peritubular capillaries (PTC) (Fig. 2).

2) Migration of granulocytes and macrophages and phagocytosis are seen during humoral rejection (Fig. 2).

3) In the case of fulminant humoral rejection, thrombi occurs even in the main renal arteries, and this results in necrosis and infarction in renal tissues.

Others

ABO-blood group glycosyltransferase is transiently produced in transplanted kidneys.

2. Reasons why local (intrarenal) DIC is thought to underlie humoral rejection

Humoral rejection in ABO-incompatible kidney transplantation, as based on the above-listed findings, is likely due to the following:

Serum antibody titer (determined by the saline method, the indirect Coombs test, and the bromelin method) decreases to almost 0 for several days after transplantation in almost all incompatible transplantations. Furthermore, a one-hour biopsy (taken 1 hour after reperfusion following transplantation), but not

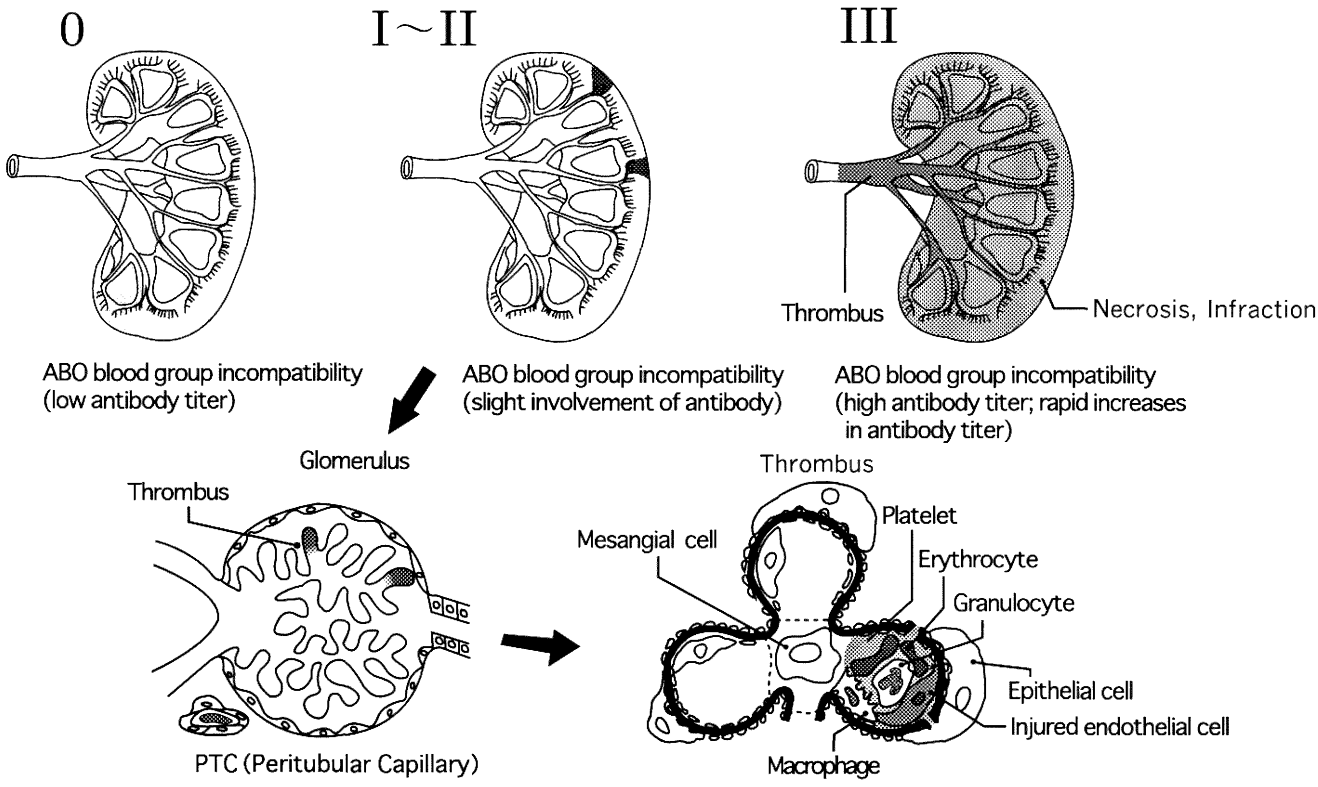


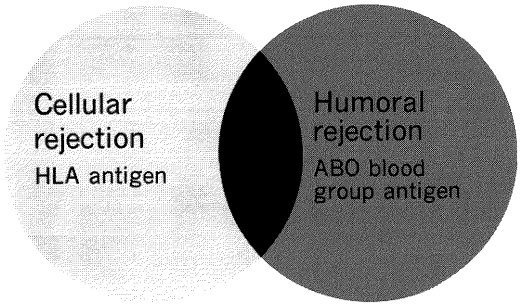
Fig. 2. Degree of humoral rejection due to ABO blood group antigen (intrarenal DIC).

a 0-hour biopsy (taken before reperfusion), both obtained from kidneys removed from donors, occasionally show thrombi in Henle's loops and PTC, erythrocyte rouleaux formation, and granulocyte migration (Fig. 2).

Anti-A and anti-B antibodies adhere to blood group antigens on vascular endothelial cells, triggering antigen-antibody reactions, which cause endothelial cell injury. This, in its turn, induces production of cytokines, migration factors, and free radicals, which activate platelets and complements, and induce thrombi, migration of granulocytes and macrophages, and phagocytosis (Fig. 1). Endothelial cell injury may be enhanced by reperfusion disorders when blood flow blockage is removed (Fig. 1).[25] These changes are thought to cause subclinical rejection reactions which are quickly repaired but easily recur. (Fig. 2, I-II).

Clinical signs and symptoms associated with typical acute rejection reactions seen at an early period after incompatible kidney transplantation include a high fever of 38℃ and over, thrombocytopenia, and swelling of the graft. Fever is thought to be due to lymphokines generated by the thrombi and vasculitis. Lymphokines could also be responsible for renal inflammation. Swelling is thought to be attributable to edema due to circulatory insufficiency.

Antibody titer does not increase much as long as antibodies are adsorbed to the kidneys, and humoral rejection is added to cellular rejection in almost all cases of acute rejection seen within 1 month after transplantation. Evidence of humoral rejection is always observed in graft loss seen at this early period. In addition, the degree of cellular rejection is not necessarily correlated with that of humoral rejection. It is not unusual for cellular rejection to be slight while humoral rejection is so severe as to be associated with interstitial hemorrhage. This observation is critical, because in cellular rejection, recipients' lymphocytes recognize donors' different HLA antigens and infiltrate into renal tubules and the interstitial space. Local DIC triggered by antigen-antibody reactions is a condition which underlies humoral rejection, and similar mechanisms can be postulated for humoral rejection seen in anti-T cell antibody-positive transplantation and xenotransplan-



Type of rejection	Cellular rejection	Humoral rejection (Intrarenal DIC)
Tissues mainly affected	Renal tubules and interstitial space	Vascular endothelial cell • Henle's loop • PTC (Peritubular Capillary) • Blood vessel
Pathological findings	Lymphocyte infiltration	(1) Thrombus (2) Granulocyte migration and macrophage phagocytosis

Fig. 3. Kidney transplantation rejection due to ABO blood group incompatibility.

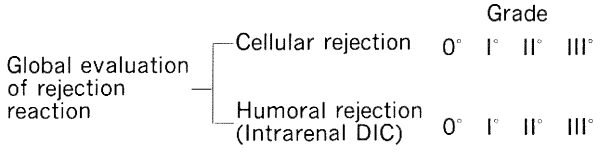


Fig. 4. Classification of rejection reactions.

tation (Fig. 3).

In Banff's classification system, rejection associated with vasculitis is classified as severe. However, this system does not clearly separate cellular and humoral rejections. We believe that cellular and humoral rejections should be separated and independently graded, and that global assessment should be made taking into account the grade of both cellular and humoral rejections (Fig. 4).

The degree of renal tissue impairment due to humoral rejection is determined by various factors, including the amount of antibodies (antibody titer), the degree of vascular endothelial cell injury, and the site of injury in blood vessels (arteries). In the presence of a small amount of antibodies, thrombi are formed in a portion of peripheral blood vessels (Henle's loops and PTC), and, as associated minor lesions are repeatedly produced and repaired, more significant changes such as circulatory insufficiency, thickening of vascular intima, vascular stenosis, and arteriosclerosis, and ultimately chronic rejection occur. In the presence of a large amount of antibodies, where a large amount of blood-group antigens is present per ml of blood, thrombi formed in fine blood vessels (where the blood flow is slow) rapidly spread into thick arteries, resulting in extensive renal infarction and ultimately graft loss.

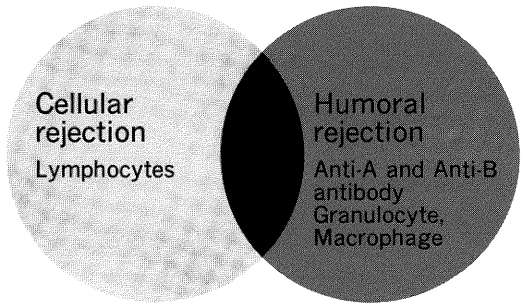
3. Immunosuppressive therapy in ABO-incompatible transplantation and anti-rejection therapy

Immunosuppressive therapy

Immunosuppressive therapy in ABO-incompatible transplantation can be classified into the following four types: 1) extracorporeal immunomodulation (elimination of natural anti-A and anti-B antibodies or humoral antibodies;[31] 2) drugs that control cellular immunity; 3) splenectomy; and 4) anticoagulation therapy. (Fig. 5).

1) Extracorporeal immunomodulation before transplantation

Anti-A and anti-B antibodies are eliminated from the patients' serum before transplantation regardless of pre-transplantation antibody titer values. Plasma exchange[3-17] and immune adsorption[32-35] are generally conducted for this purpose, and each has its own advantages and disadvantages. The former is more efficient, while the latter is more specific. In any case, pre-transplantation anti-A and anti-B antibody titer should be reduced to 8 or less in order to effectively inhibit humoral rejection. The lower the antibody



Treatment of Cellular rejection
1. Pharmacotherapy
   • Steroid pulse therapy
   • ALG
   • Muromonab CD3 (OKT3)
   • DSG

Treatment of Humoral rejection
1. Antibody elimination, plasma exchange and immune adsorption
2. Anti-DIC therapies
   -Anticoagulants: heparin (including low-molecular-weight heparin)
   -Synthetic protease inhibitors: gabexate mesilate (FOY) and nafamostat mesilate (FUT)
   -Blood preparation: dried ATIII concertrate
3. Pharmacotherapy
   -Steroid pulse therapy
   -Muromonab CD3 (OKT3)
   -DSG
   -Immunodulators: sodium aurothiomalate
      auranofin
      bucillamine

Fig. 5. Treatment of rejection.

titer, the better.

2) Pharmacotherapy

In incompatible kidney transplantation, rejection often results in graft loss if it occurs at an early period after transplantation. We therefore conduct a more rigorous initial immunosuppressive therapy in incompatible transplantation than in compatible transplantation. In the maintenance period following this critical period, humoral rejection is less likely to occur; thus, types and doses of immunosuppressive agents used in both types of transplantation do not differ. It is of particular importance to effectively inhibit T lymphocytes shortly after transplantation; however, the inhibition of B lymphocytes, which are involved in the production of humoral antibodies, is also essential. In general, multiple drug therapy is undertaken combining steroids, ciclosporin, tacrolimus (FK506),[36] azathioprine (AZ), mizoribine (MZ), mycophenolate mofetil (MMF),[37] antilymphocyte globulin (ALG), deoxyspergualin (DSG).[9,38,39] At present, we combine methylprednisolone (MP), FK506, and AZ for immunosuppression at the induction period and add ALG for 2 weeks after transplantation.[40]

3) Splenectomy

As shown by Salamon et al.,[41] the spleen greatly contributes to the production of anti-A and anti-B antibodies. We therefore conduct splenectomy before or after ABO-incompatible kidney transplantation.[3-5]

4) Anticoagulation therapy

Because of extracorporeal immunomodulation conducted before transplantation, coagulation factors are lost and the bleeding tendency generally increases during the perioperative period. For this reason, anticoagulation therapy may be unnecessary or should not be very intense shortly after transplantation. In our unit, we use the platelet aggregation inhibitor ticlopidine starting 1 week after transplantation.

Antirejection therapy

As mentioned above, rejection seen shortly after transplantation is very violent, in particular accelerated acute rejection which occurs within 1 week after transplantation and in which anti-A and anti-B antibodies are involved (humoral rejection). For this reason, every effort should be made to prevent rejection at this period.

1) Treatment of cellular rejection
Policies adopted for rejection reactions in general can be applied. DSG[9,38,39] or muromonab CD3 (OKT3) should always be added to MP pulse therapy to deal with accelerated acute rejection within 1 week after transplantation. Before using OKT3, however, it is essential to ensure that B lymphocytes are suppressed. Otherwise, B lymphocytes, which are normally controlled by T lymphocytes, may be activated because OKT3 inhibits pan T lymphocytes, leading to the rapid production of anti-A and anti-B antibodies and abrupt increases in blood coagulation, which result in thrombosis and renal infarction. The same is true with strong rejection observed at an early lymphocytes after transplantation in anti-T cell antibody-positive patients. In order to prevent these adverse events, it is recommended that AZ, MZ or MMF—which inhibit B lymphocytes—be coadministered, and that OKT3 be administered after eliminating anti-A and anti-B antibodies by plasma exchange or other appropriate methods.

2) Treatment of humoral rejection
Treatment of both cellular and humoral rejections is necessary to deal with rejection reactions at an early period after incompatible transplantation because both cellular and humoral factors are always involved. As local (intrarenal) DIC underlies humoral rejection, elimination of its cause (anti-A and anti-B antibody) and anticoagulation therapy[43] are essential.
i) Elimination of the cause of local DIC (anti-A and anti-B antibodies): The cause of local DIC is anti-A and anti-B antibodies. Extracorporeal immunomodulation is therefore essential for their elimination. Plasma exchange or immune adsorption can be selected as necessary. It is critical to decrease antibody titer as soon as and as much as possible. Antibodies are easily adsorbed to vascular endothelial cells in the kidneys. Antibodies must be eliminated before serum antibody titer increases (serum antibody titer increases after antibodies are adsorbed to the kidney). The kidney is saturated with antibodies by the time the serum antibody titer shows abrupt increases, and excess antibodies are released into the serum. Efforts to eliminate antibodies initiated at this stage are useless because even thick arteries are packed with thrombi and renal tissues show necrosis and infarction.
ii) Anticoagulation therapy: I believe that the generally conducted anti-DIC therapy is effective. Anticoagulants (heparin, low-molecular-weight heparin, antithrombin III, etc.), protease inhibitors (gabexate mesilate (FOY) and nafamostat mesilate (FUT)) and platelet aggregation inhibitors (e.g., ticlopidine) are recommended.
iii) Role of granulocytes and macrophages: Histological findings obtained during humoral rejection often include the migration of granulocytes and macrophages, and phagocytosis, suggesting the presence of excessive defense reactions. Therefore, immunomodulators used in the treatment of rheumatoid arthritis such as sodium aurothiomalate, auranofin, and bucillamine may be effective, although I have not yet tried any of them. Careful studies will be necessary before their clinical application to incompatible transplantation, however, owing to their strong side effects.

Conclusion

Local (intrarenal) DIC underlies humoral rejection in ABO-incompatible kidney transplantation. In this paper, I have tried to validate this hypothesis and outlined therapeutic approaches recommended to deal with it.

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