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Antibody Mediated Acute Renal Allograft Rejection - A Unique Case

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We report here a case of acute rejection of renal transplant in a forty nine year old female. The renal biopsy showed distension of glomerular capillaries with thrombi. The morphological features suggest accelerated antibody mediated rejection process despite negative cross match. Similar phenomenon noted earlier by other authors has been attributed to endothelial antigen involvement. However, this phenomenon is distinctly rare.

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Acute renal allograft rejection continues to affect the survival of nearly 27% of living related transplants and 30% of cadaver transplants despite the careful pre and post transplant care and strict application of protocols[1]. Acute rejection events occurring within 60 days of transplantation carry bad prognosis for the long term survival of the allograft, however, vigorous the anti-rejection therapy may be. We report a case of acute renal allograft rejection in 46 years old Bahraini female. Histopathological analysis proved to be accelerated antibody mediated rejection with negative cross match.

THE CASE

Forty six year old Bahraini female underwent renal transplant on November 30th 1999 for end stage renal disease secondary to hypertension. The donor was her healthy daughter. The Human Leucocyte Antigen (HLA) profile of the patient and the donor was as follows:

HLA- Patient A11 A33 (19) B7 - B52 (5) BW4 - BW6
CW7 DR16 (2) - DR9, DR51
DQ5 (1) - DQ2

HLA- Donor A26 (10) - A33 (19). B7 - B38 (16), BW4 -BW6
CW4 - CW7, DR16 (2) - DR14 (6)
DR51 - DR52, DQ5 (1)

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The pre-transplant investigations included negative T cell B cell cross match, autocross match and T cell cross match by flowcytometery. The patient was screened for ANA, ADNA, CMV antibody, HbsAg, Anti-HCV, Anti-HIV which were negative. No G_6PD deficiency or electrophoretically detectable hemoglobinopathy was noticed. The immunosuppressent regimen was one dose of Interleukin (IL) -2 receptor antibody during surgery, followed by cyclosporine, azathioprine and methyl prednisolone.

Postoperatively, the patient had a spike of fever with lowering of urine output which improved with intravenous fluids. Later, the hemoglobin and platelet count dropped below 9 gm/dl and 178 x 10^9 / litre respectively.

The following day, the hematological and biochemical parameters showed further deterioration, Hb dropped to 7.7 gm/dl, Platelet count dropped to 40x 10^9 /litre, WBC 14.7 x 10^9 /litre (Polymorphs 87%; Lymphocytes 9%; Monocytes 1%; Band cells 2%; myelocyte 1%; reticulocyte count 1%). The peripheral blood smear showed fragmented red cells, burr cells and polychromatophilic red cells. There was no improvement in serum creatinine where it remained at 280micro mol /litre. Coomb's test was negative. Urine analysis revealed massive proteinuria and 7-8 red blood cells/ high power field. The patient received platelet transfusion followed by plasmapheresis on 3-12-1999. In spite of this, serum creatinine increased to 300 micro mol/ litre. An open renal biopsy of the allograft was taken and at the operation the graft was congested, oedematous and swollen.

Histopathology revealed over 30 glomeruli in the biopsy specimen and all were distended with platelet thrombi (Figure 1). The tubular lumen showed red cell and protein casts. The stroma was oedematous. There was no tubulitis or vasculitis. Based on the morphology, a diagnosis of accelerated acute antibody rejection (Banff 2 B) was made. At this stage, a repeat TB cell cross match was done which proved to be negative again. Cyclosporine, azathioprine and co-trimoxazole were withdrawn gradually. Mycophenolate mofetil and methyl prednisolone were included. Plasmapheresis continued, but renal dysfunction persisted. The patient was maintained in non-oliguric phase with frusemide. On the 5^{th} post-operative day, the patient needed haemodialysis and ultra filtration for fluid overload and azotemia. The platelet count rose to 100 x10^9/litre, the hemoglobin level remained below 5gm/dl with fragmented red cells in the peripheral blood. A second dose of IL-2 receptor antibody was administered as scheduled. Pulse doses of methyl prednisolone were given.

Figure 1. Glomeruli distended with platelet thrombi. H & E x 400

A second biopsy was taken on 12-12-1999 because there was no improvement in the renal function and uncontrolled hypertension. The renal biopsy at this stage showed similar glomerular pathology as in the previous biopsy, but less in severity. There was tubulitis (Figure 2) in more than 25% of the tubular compartment involving more than 10% of the parenchyma. There was 25% endotheilitis in the one artery in the biopsy. The morphological diagnosis was acute rejection Banff 4II B. The graft function improved temporarily, but deteriorated gradually in the next four months with persistent renal dysfunction and uncontrolled hypertension. The patient succumbed to the illness in May 2000.

Figure 2. Microscopic picture of tubulitis of Banff 4IIB. H & E x 400

DISCUSSION

This patient showed clinical features of accelerated acute rejection (antibody related) followed by acute rejection of type 4IIB characterized by tubulitis and endotheilitis[5]. The pre and post transplant screening for any donor specific antibody was negative.

Trpkov, et al[2] analysed 44 biopsies which proved to be acute renal allograft rejections and found 20 cases to be negative for antibody against donor class I antigens. They reported tubulitis occurring more frequently in antibody negative patients with over 95% patients exhibiting moderate to severe tubulitis. The vascular rejections were associated with the presence of anti-Class I antibodies of the donor. Onitsuka[3] observed tubulitis as a dominant feature in the acute rejection of ABO compatible renal transplantation and associated with high expression of HLA class II (DR) and adhesion molecules (ICAM-1 and VCAM-1).

These findings does not support the present case as it is accelerated acute rejection characterized by glomeruli distended with platelet and fibrin thrombi. The pathogenesis in this situation appears to be different.

Demirhan, et al[4] reported hyper acute allograft rejection similar to this case with a negative lymphocyte cross match. The two cases reported had shown all features of hyper acute allograft rejection despite negative lymphocyte cross match. Citing similar cases from the literature, these investigators considered anti-vascular endothelial cell antibody

possibly were responsible for hyper acute allograft rejection. As vascular endothelial antigens are not completely well defined, there is no available screening test to identify them. Hence, it is to be noted that antibody mediated acute rejections may be encountered rarely despite compatible HLA antigens and negative cross match.

CONCLUSION

The present case illustrates the antibody mediated accelerated renal graft rejection in a 49 year old female. The pretransplant work up did not reveal any major mismatch in the antigen profile between the donor and the recipient who are blood related. The histology revealed glomerular capillary distension with platelet thrombi, which is the hallmark of antibody-mediated rejection. The unique finding of negative cross match with histological alterations and the rapid deterioration in renal function support the rare antibody mediated accelerated rejection due to the possible vascular endothelial antigens.

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