RENAL TRANSPLANT REJECTION

HYPERACUTE REJECTION

Hyperacute rejection may occur within minutes or hours after revascularization, with the immediate result being the abrupt cessation of urine flow. The rejection is produced by the interaction of preformed circulating antiboies in the recipient with antigens on donor endothelial cells. The antibodies are often related to previous kidney transplant. The introduction of routine transplant screening and cross-matching techniques has made this a rare complication.

In hyperacute rejection, fibrin thrombi are present in all the renal vessels including the glomerular capillaries and peritubular venules. The thrombosis is associated with infarction and tubular necrosis and there is a variable infiltrate of leukocytes within the glomeruli, peritubular capillaries and interstitium. Immunofluorescence show linear staining for IgM or Igg and C3 along the glomerular and pertibular capillaries.

ACUTE REJECTION

Can occur at any time during the course of transplantation. It is most often seen in the months following grafting and becomes less common after the first year. Two reaction patterns can be seen: vascular and interstitial.

A. Vascular rejection, also termed acute humoral rejection, the most severe changes occur in the small arteries, veins and arterioles. The earliest morphologic indication of acute vascular rejection is swelling and vacuolization of the endothelial cells with areas of ulceration. This is usually associated with intimal infiltration by mononuclear inflammatory cells and by changes in the media. Individual smooth muscle cells show vacuolization caused by dilatation of the endoplastic reticulum. The intimal changes can be accompanaied by either thrombosis or intimal changes can be accompanied by thrombosis or intimal proliferation.

   Occasionally, a pattern of acute necrotizing vasculitis may be seen. The glomeruli show endothelial cell swelling, an increase in cellularity and occasional thrombosis. Interstitial hemorrhage, tubular necrosis and infarction are also seen.

B. Acute interstitial allograft rejection

It has also been called cellular rejection, acute tubulointerstitial or acute reversible rejection. It reveals edema and focal infiltration of the interstitium and peritubular capillaries by lymphoc ytes. As the rejection progresses, the inflammatory infiltrate becomes more diffuse and the lymphocytes, many of them immunoblasts, plasma cells, monocytes and macrophages.

Eosinophils can also be present, but rarely in large numbers. A characteristic finding in acute interstitial rejection is invasion of the tubular epithelial cells by lymphocytes producing a lesion referred to as tubulitis. Tubulitis has been regarded as a reliable marker for acute rejection even though it can be seen in other forms of interstitial nephritis. The intensity of the infiltrate and tubular injury are features often used to grade the rejection. The infiltrate is more concentrated in the cortex than in the renal medulla. Immunophenotyping shows that most the lymphoid cells are T lymphocytes as 60 to 80% are CD8 positive cells, the remainer being CD4 positive T lymphocytes, plasma cells and monocyte/macrophages. Immunofluorescence is generally negative.

CHRONIC REJECTION

Chronic rejection may occur at any time from several months to several years after transplantation and once irritated as irreversible. It constitutes the most common cause of graft failure after he initial 6 to 12 months. Chronic rejection is not a distinct entity with a specific pathogenesis, but rather the end stage of repeated episodes of acute vascular or interstitial rejection. In addition, long-term administration of cyclosporine A or tacrolimus probably contributes to the development of some of the changes seen in chronic rejection. Clinically, there is a gradual decrease in renal function. The deterioration may be preceded by proteinuria, sometimes with the nephrotic syndrome and is commonly associated with hypertension. Microscopically, the picture is similar to that seen in nephrosclerosis. The blood vessels, especially the interlobular and acruate arteries, show severe obliterative fibrointimal proliferation or mucoid widening of the intima. Reduplication or disruption of the elastic lamina and irregular fibrosis of the media are also common. The distribution of the vascular lesions is irregular and some blood vessels appear normal while others present lesions of variable degrees of severity. Small thrombi in various stages of organization can be found. Tubules are atrophic and the interstitium is diffusely scarred. The glomerular lesions consist of ischemic glomerular capillary collapse, thickening of the capillary walls and segmental and global sclerosis.

The Banff classification

The best known was formulated by an international group of renal pathologists, nephrologists and transplant surgeons and was published in 1993.

Banff 97 diagnostic categories for renal allograft biopsies

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1. Normal.
2. Antibody-meidated rejection.
   A] Immediate (hyperacute)
   B] Delayed (accelerated acute)
3. Boderline changes: " Suspicious" for acute rejection. Cases with foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section) and interstitial inflammation (10% to 25% of parenchyma affected).
4. Acute/active rejection.
   Type IA: Cases with significant interstitial inflammation (>25%) of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells).
   Type IB: Cases with significant interstitial ainflammation (> 25% of parenchyma affected) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section of group of 10 tubular cells).
   Type IIA: Cases with mild to moderate intimal arteritis (v1).
   Type IIB: Cases with severe intimal arteritis comprising > 25% of the luminal ares (v2).
   Type III: Cases with 'transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (v3 with accompanying lymphocytic inflammation).
5. Chronic/sclerosing allograft nephropathy.
   Grade I: mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection.
   Grade II: moderate interstitial fibrosis and tubular atrophy (a) or (b).
   Grade III: Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b).
6. Changes unrelated to rejection.

CYCLOSPORIN TOXICITY

Is an immunosuppressant drug that is extremely effective in controlling transplant rejection; unfortunately, however, it is nephrotoxic. It also include hepatoxicity, gingival hyperplasia, hypertrichosis, and malignancies, particularly lymphomas. Nephrotoxicity is dose related and has been classified into functional toxicity in which there are no structural changes and morphologic forms in which the toxicity is manifested by a variety of lesions affecting tubules, vessels and renal interstitium. Three major morphologic forms are recognized: acute nephrotoxicity, chronic nephrotoxicity and thrombotic microangiopathy.

Functional toxicity

Functional CsA toxicity probably affects every patient who receives this medication. A mild decrease in renal function and a mild elevation of serum creatinine levels are seen soon after therapy status, but both are reversible if the dosage is reduced. Hypertension is seen in up to 50% of the patients. Renal biopsies in these patients appear normal or at most show some dilatation and congestion of peritubular capillaries. The pathogenesis is an alteration of intrarenal hemodynamics that results from the ability of CsA to induce intense renal vasoconstriction.

Acute toxicity

The clinical manifestations are similar to those of functional toxicity but tend to be more severe. The lesion is characterized by vacuolization of the proximal tubules, often in an isometric pattern with giant mitochondria, large lysosomes and microcalcifications. Electron microscopic studies have demonstrated that the vascuolization is the result of dilatation of the endoplasmic reticulum.

Thrombotic microangiopathy

Patients with CsA toxicity can develop symptoms similar to those of hemolytic uremic syndrome. The histologic findings are those of thrombotic microangiopathy with platelet and fibrin thrombi in the glomeruli and vessels and minimal inflammatory infiltrate. The prognosis of these patients is generally poor, but in some instances the lesions have resolved after the drug has been withdrawn.

Chronic toxicity

Chronic CsA toxicity is clinically manifested by slow progression to renal failure and hypertension. Biopsies show arteriolopathy and interstitial fibrosis with tubular atrophy. The arteriolopathy consists of nodular or diffuse hyalinosis or the vessel walls or mucoid thickening of the intima, resulting in narrowing or complete

occlusion of the vascular lumen. The changes are usually accompanied by focal interstitial fibrosis. The glomeruli are usually spared in the early stages, although the capillaries may contain aggregates of platelets and fibrin. In contrast to acute nephrotoxicity, the changes in chronic nephrotoxicity are irreversible.

Tacrolimus (FK506) toxicity

Tacrolimus is new immunosuppressant drug used in the control of transplant rejection. The morphologic changes associated with tacrolimus toxicity are similar to those of CsA toxicity.