Transplantation as Treatment of End-Stage Renal Disease

FIGURE 9-4
Histologic features of acute accelerated rejection. A and B. Photomicrographs showing histologic features of acute accelerated vascular rejection. Glomerular and vascular endothelial infiltrates and swelling are visible. An accelerated rejection, which may start on the second or third day, tends to occur in the previously sensitized patient in whom preformed anti-HLA antibodies are present. This type of rejection occurs in patients who have had a previous graft and presents with a decrease in renal function; the clinical picture is similar to that for hyperacute rejection.

FIGURE 9-5
Histologic features of acute cellular rejection. A, Mild tubulitis. B, Moderate to severe tubulitis. Acute rejection episodes may occur as early as 5 to 7 days, but are generally seen between 1 and 4 weeks after transplantation. The classic acute rejection episode of the earlier era (ie, azathioprine-prednisolone) was accompanied by swelling and tenderness of the kidney and the onset of oliguria with an associated rise in serum creatinine; these symptoms were usually accompanied by a significant fever. However, in patients who have been treated with cyclosporine, the clinical features of an acute rejection are really quite minimal in that there is perhaps some swelling of the kidney, usually no tenderness, and there may be a minimal to moderate degree of fever. Because such an acute rejection may occur at a time when there is a distinct possibility of acute cyclosporine toxicity, the differentiation between the two entities may be extremely difficult.

The differential diagnosis of acute rejection, acute tubular necrosis, and cyclosporine nephrotoxicity may be difficult, especially in the early posttransplant period when more than one cause of dysfunction can occur together [2]. Knowledge of the natural history of several clinical entities is extremely helpful in limiting the differential diagnosis. Reversible medical and mechanical causes should be excluded first. Percutaneous biopsy of the renal allograft using real-time ultrasound guide is a safe procedure. It provides histologic confirmation of the diagnosis of rejection, aids in the differential diagnosis of graft dysfunction, and allows for assessment of the likelihood of a response to antirejection treatment.
Transplant Rejection and its Treatment

Acute rejection
Antibody deposition
Oxidized LDL
Infection
T cells
Macrophages
Platelet aggregates
Cytokines/growth factors
Cell proliferation
Fibrosis
Reduced nephron mass
Graft loss
Vascular injury
Arteriosclerosis
Tubulointerstitial injury
Glomerular sclerosis

C. CHRONIC ALLOGRAFT REJECTION

Typical clinical presentation
Gradual increase in creatinine (months)
Non-nephrotic-range proteinuria
No recent nephrotoxic events
Key pathologic features
Interstial fibrosis
Arterial fibrosis and intimal thickening

D. The likely sequence of events in chronic rejection and potential mediating factors for key steps. Progressive azotemia, proteinuria, and hypertension are the clinical hallmarks of chronic rejection. Immunologic and nonimmunologic mechanisms are thought to play a role in the pathogenesis of this entity. Immunologic mechanisms include antibody-mediated tissue destruction that occurs possibly secondary to antibody-dependent cellular cytotoxicity leading to obliterative arteritis, growth factors derived from macrophages and platelets leading to fibrotic degeneration, and glomerular hypertension with hyperfiltration injury due to reduced nephron mass leading to progressive glomerular sclerosis. Nonimmunologic causes can also contribute to the decline in renal function. Atheromatous renovascular disease of the transplant kidney may also be responsible for a significant number of cases of progressive graft failure.

FIGURE 9.6
Features of chronic rejection. A, Arterial fibrosis and intimal thickening. B, Interstitial fibrosis and tubular atrophy. C, Typical presentation and pathologic features. Chronic rejection occurs during a span of months to years. It appears to be unresponsive to current treatment and has emerged as the major problem facing transplantation [5]. Because chronic rejection is thought to be the end result of uncontrolled repetitive acute rejection episodes or a slowly progressive inflammatory process, its onset may be as early as the first few weeks after transplantation or any time thereafter.

(Continued on next page)
Transplantation as Treatment of End-Stage Renal Disease

### FIGURE 9-7

The Banff classification of renal allograft rejection. This schema is an internationally agreed on standardized classification of renal allograft pathology that regards intimal arteritis and tubulitis as the main lesions indicative of acute rejection [6].

### BANFF CLASSIFICATION OF RENAL ALLOGRAFT REJECTION

- **Normal**
  - Patchy mononuclear cell infiltrates without tubulitis is not uncommon
- **Borderline changes**
  - No intimal arteritis; mild tubulitis and endocapillary glomerulitis
- **Acute rejection**
  - Grade I: tubulitis ++
  - Grade II: tubulitis with glomerulitis
  - Grade III: intimal arteritis, interstitial hemorrhage, fibrinoid, thrombosis

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**Diagnostic and therapeutic approach to chronic rejection**

1. Slowly rising creatinine
   - Check CsA level
     - **High**
       - Lower CsA dose and repeat creatinine
         - Improved
         - No improvement
     - **Low**
       - Ultrasound
         - **Obstruction**
         - **No obstruction**
         - Biopsy
           - Rejection
             - **Acute**
             - **Acute on chronic**
             - **Chronic**
               - Adjust immunosuppressant
                 - Steroid bolus
                 - OKT3 or ATG
               - Temporizing measures
                 - Control BP
                 - Avoid nephrotoxins
     - **ATN**
       - Glomerulonephritis
       - Recurrent GN
       - de novo GN

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**FIGURE 9-6 (Continued)**

E, Diagnostic and therapeutic approach to chronic rejection. ATG — antithymocyte globulin; ATN — acute tubular necrosis; BP — blood pressure; CsA — cyclosporine; LDL — low-density lipoprotein.