the graft and recognize graft antigens being displayed by host APCs that have also entered the graft, and the result is a delayed hypersensitivity type of inflammatory reaction. However, CD8+ CTLs that may be generated by the indirect pathway cannot kill graft cells, because these CTLs recognize graft antigens presented by the host's APCs and cannot recognize the graft cells directly. Therefore, when T cells react to a graft by the indirect pathway, the principal mechanism of cellular rejection may be T-cell cytokine production and inflammation.

The frequency of T cells that can recognize the foreign antigens in a graft is much higher than the frequency of T cells specific for any microbe. For this reason, immune responses to allografts are stronger than responses to pathogens. Predictably, these strong reactions can destroy grafts rapidly, and their control requires powerful immunosuppressive agents.

B lymphocytes also recognize antigens in the graft, including HLA and other antigens that differ between donor and recipient. The activation of these B cells typically requires T cell help.

T Cell–Mediated Reactions

The critical role of T cells in transplant rejection has been documented in humans and in experimental animals. T cells can contribute to both acute and chronic rejection.

- **Acute cellular rejection,** also called *acute T cell–mediated rejection*, is most commonly seen within the initial months after transplantation and is heralded by clinical and biochemical signs of organ failure. It was thought that direct killing of graft cells by CD8+ CTLs is a major component of the reaction. However, more recent studies have established that an important component of this process is an inflammatory reaction in the graft triggered by cytokines secreted by activated CD4+ T cells. The inflammation results in increased vascular permeability and local accumulation of mononuclear cells (lymphocytes and macrophages), and graft injury is caused by the activated macrophages.
- T cells also contribute to **chronic rejection,** in which lymphocytes reacting against alloantigens in the vessel wall secrete cytokines that induce local inflammation and may stimulate the proliferation of vascular endothelial and smooth muscle cells.

Antibody-Mediated Reactions

Although T cells are pivotal in the rejection of organ transplants, antibodies produced against alloantigens in the graft are also important mediators of rejection. Antibody-mediated reactions can take three forms.

- **Hyperacute rejection occurs when preformed antidonor antibodies are present in the circulation of the recipient.** Such antibodies may be present in a recipient who has previously rejected a transplant. Multiparous women who develop antibodies against paternal HLA antigens shed from the fetus may have preformed antibodies that will react with grafts taken from their husbands or children, or even from unrelated individuals who share HLA alleles with the husbands. Prior blood transfusions can also lead to presensitization, because platelets and white blood cells are rich in HLA antigens and donors and recipients are usually not HLA-identical. Hyperacute rejection was a concern in the early days of kidney transplantation, but with the current practice of cross-matching, that is, testing recipient's serum for antibodies against donor's cells, it is no longer a significant clinical problem.
- **Acute antibody-mediated rejection** is caused by antidonor antibodies produced after transplantation. In recipients not previously sensitized to transplantation antigens, exposure to the class I and class II HLA antigens of the donor graft, as well as other antigens that differ between donor and recipient, may evoke antibodies. The antibodies formed by the recipient may cause injury by several mechanisms, including complement-dependent cytotoxicity, inflammation, and antibody-dependent cell-mediated cytotoxicity. The initial target of these antibodies in rejection seems to be the graft vasculature.
- **Chronic antibody-mediated rejection** usually develops insidiously, without preceding acute rejection, and primarily affects vascular components. Antibodies are detected in the circulation but are not readily identified within the graft. The mechanisms of the vascular lesions are not well understood.

Rejection of Kidney Grafts

Because kidneys were the first solid organs to be transplanted and more kidneys have been transplanted than any other organ, much of our understanding of the clinical and pathologic aspects of solid-organ transplantation is based on studies of renal allografts.

MORPHOLOGY

On the basis of the morphology and the underlying mechanism, rejection reactions are classified as hyperacute, acute, and chronic. The morphologic changes in these patterns are described later as they relate to renal transplants. Similar changes may occur in any other vascularized organ transplant and are discussed in relevant chapters.

Hyperacute Rejection

This form of rejection occurs within minutes or hours after transplantation. A hyperacutely rejecting kidney rapidly becomes cyanotic, mottled, and flaccid, and may excrete a mere few drops of bloody urine. Immunoglobulin and complement are deposited in the vessel wall, causing endothelial injury and fibrin-platelet thrombi (Fig. 6-33). Neutrophils rapidly accumulate within arterioles, glomeruli, and peritubular capillaries. As these changes become diffuse and intense, the glomeruli undergo thrombotic occlusion of the capillaries, and fibrinoid necrosis occurs in arterial walls. The kidney cortex then undergoes outright necrosis (infarction), and such nonfunctioning kidneys have to be removed.

Acute Rejection

This may occur within days of transplantation in the untreated recipient or may appear suddenly months or even years later, after immunosuppression is tapered or terminated. In any