GRAFT REJECTION

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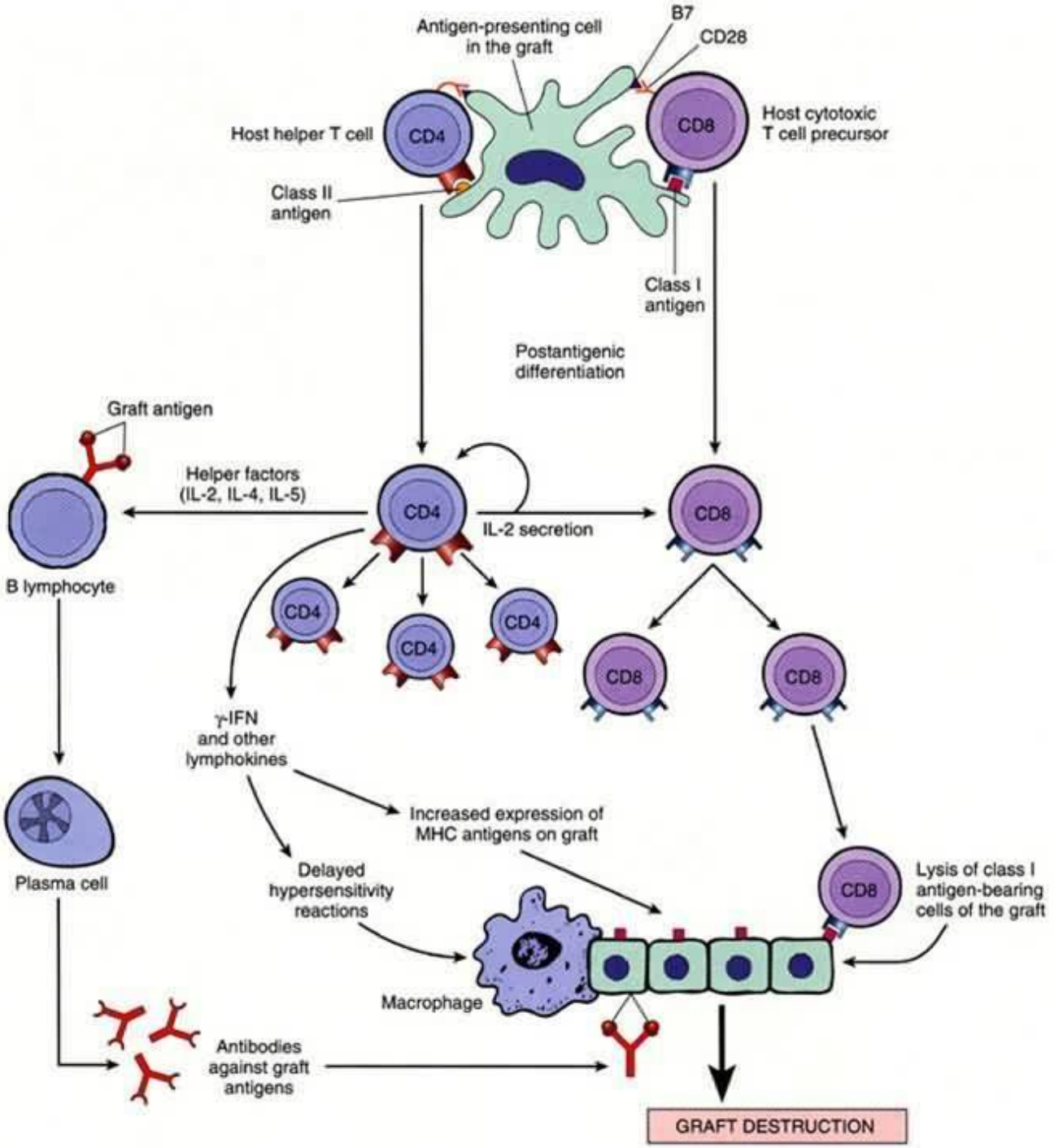
VMCH&RI

Transplant rejection

Mechanisms of transplant rejection

- T cell mediated cellular
  - **Direct pathway** via recipient CD4+ and CD8+ recognition of MHC Class I antigens on donor APCs
  - **Indirect pathway** whereby processing of antigen by the recipient's APCs is required
- Antibody mediated

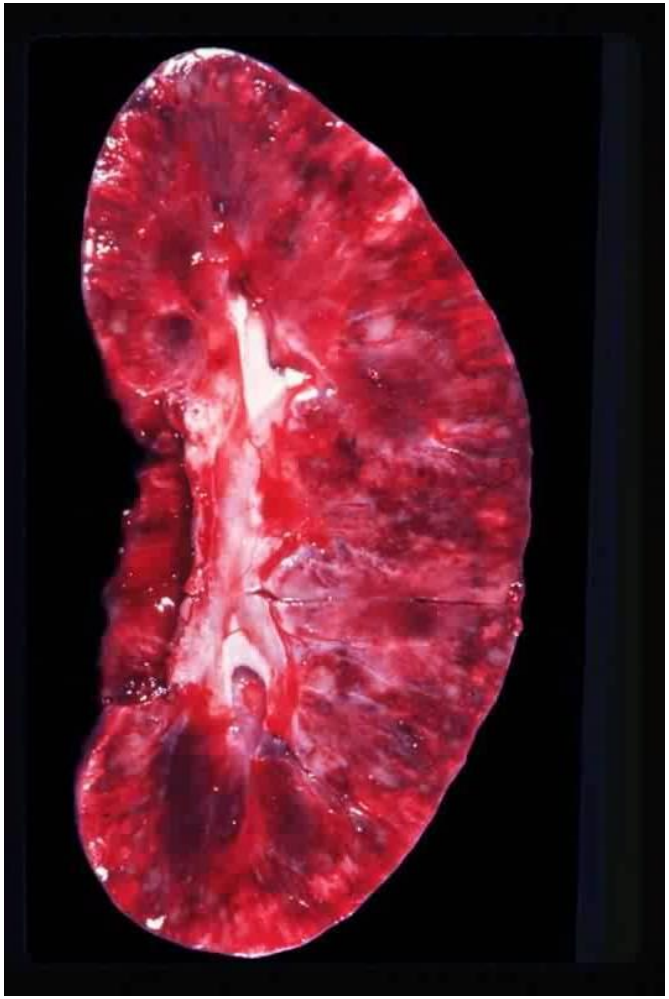

Antigen-presenting cell in the graft
B7
CD28
Host helper T cell
CD4
CD8
Host cytotoxic T cell precursor
Class II antigen
Class I antigen
Postantigenic differentiation
Graft antigen
Helper factors (IL-2, IL-4, IL-5)
CD4
IL-2 secretion
CD8
B lymphocyte
CD4
CD4
CD4
CD8
CD8
γ-IFN and other lymphokines
Increased expression of MHC antigens on graft
Plasma cell
Delayed hypersensitivity reactions
CD8
Lysis of class I antigen-bearing cells of the graft
Macrophage
Antibodies against graft antigens
GRAFT DESTRUCTION

Types of transplant rejection

- **Hyperacute:** due to preformed antibodies,
  - multiparous women/ those with an earlier transplant/ multiple transfusion history
  - Has become rare because of pre-transplant antibody screening
- **Acute:** Mixed antibody and T-cell response, usually controlled adequately by therapy
- **Chronic**: Rejection occurs months to years post-transplant and less well controlled by therapy

Hyperacute Rejection

- Occurs within minutes
- Grossly kidney purple and swollen, soft & flabby
- Widespread acute arteritis and arteriolitis
- Thrombosis of vessels, Ischemic necrosis
- Results in loss of graft



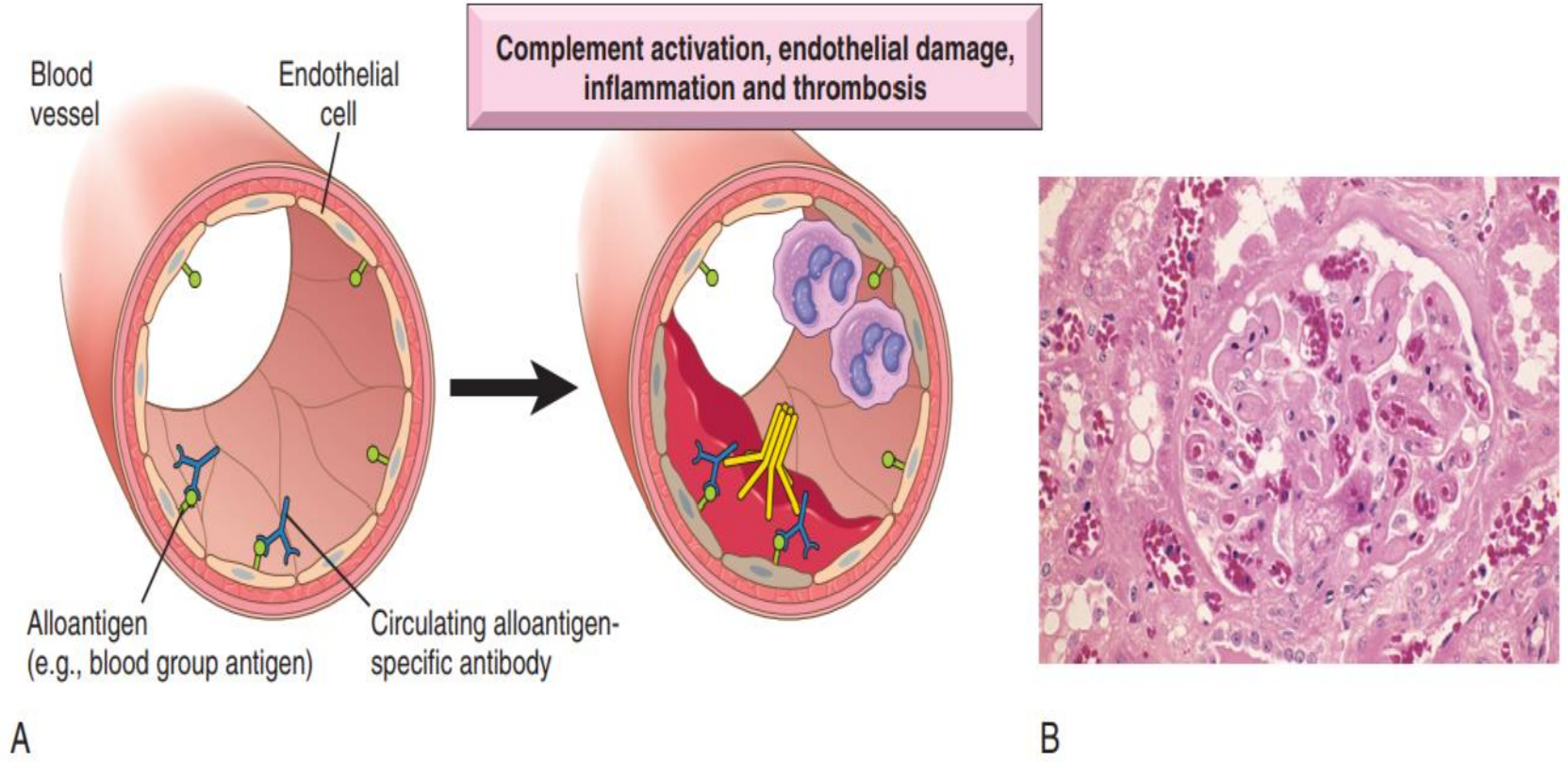


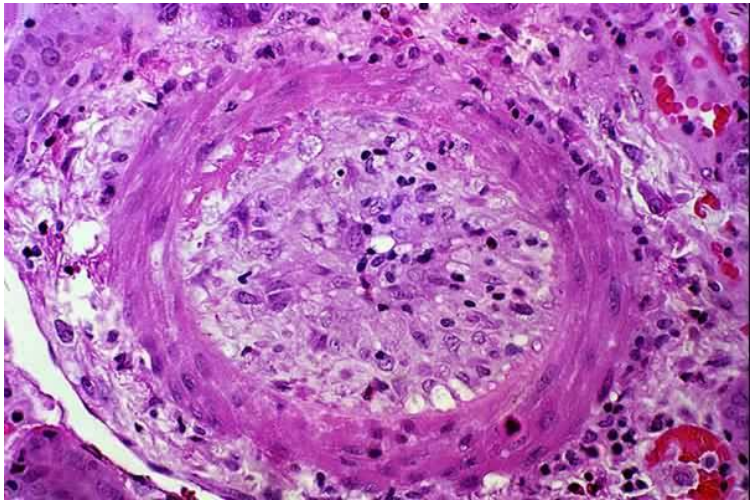
Fig. 5.31 Hyperacute rejection. (A) Deposition of antibody on endothelium and activation of complement causes thrombosis. (B) Hyperacute rejection of a kidney allograft showing platelet fibrin thrombi and severe ischemic injury in a glomerulus.

MORPHOLOGY

In hyperacute rejection, the affected kidney rapidly becomes cyanotic, mottled, and anuric. Virtually all arterioles and arteries exhibit acute fibrinoid necrosis of their walls and narrowing or complete occlusion of their lumens by thrombi (Fig. 5.31B). Neutrophils rapidly accumulate within arterioles, glomeruli, and peritubular capillaries. As these changes intensify and become diffuse, the glomerular capillaries also undergo thrombotic occlusion, and eventually the kidney cortex undergoes outright necrosis (infarction). Affected kidneys are nonfunctional and have to be removed.

Acute Rejection

- Occurs as early as 10-14 days. May occur months to years later.
- Decreased renal function. May have fever and tenderness of the graft.

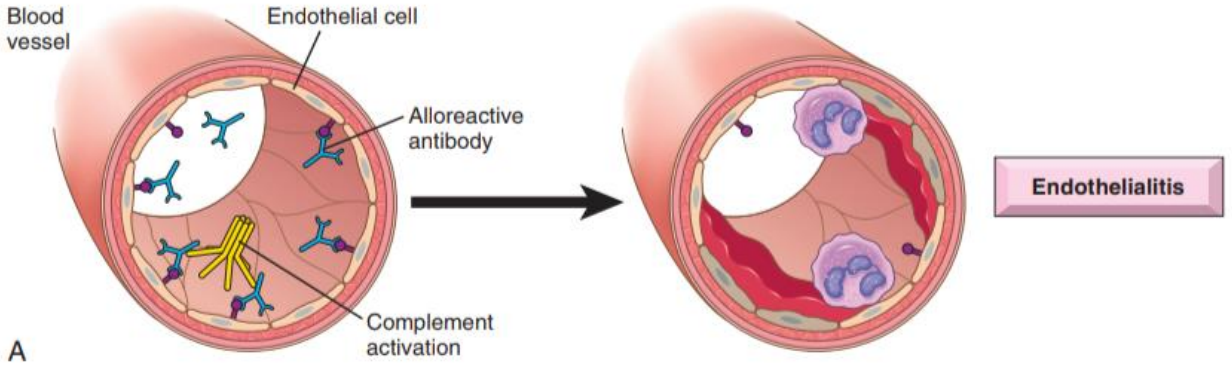


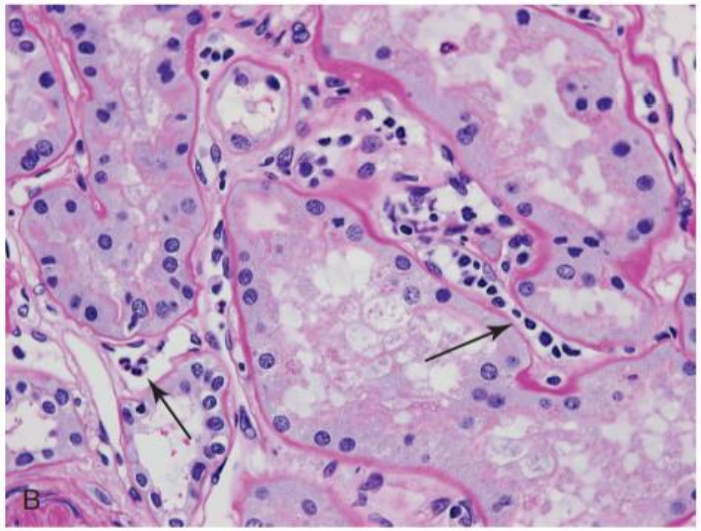
Cellular or vascular

Vascular:

- Humorally (Ab) mediated
- Vascular inflammation –
  - Necrotizing vasculitis (rejection vasculitis); sometimes thickening & fibrosis
- Responds ***less well*** to therapy

Acute Antibody mediated Rejection





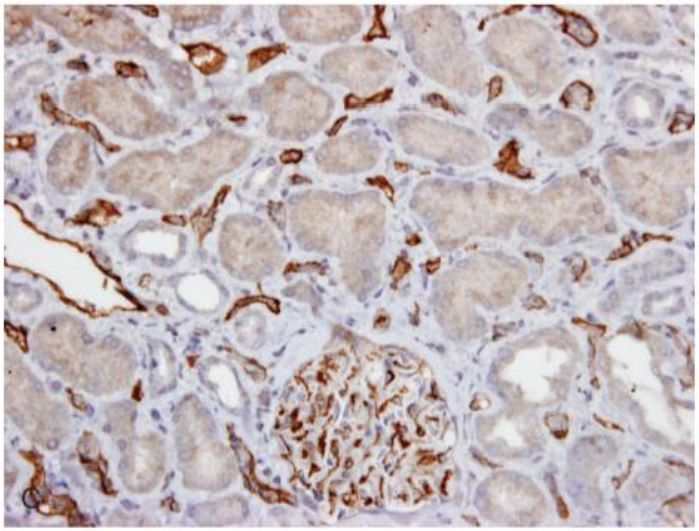


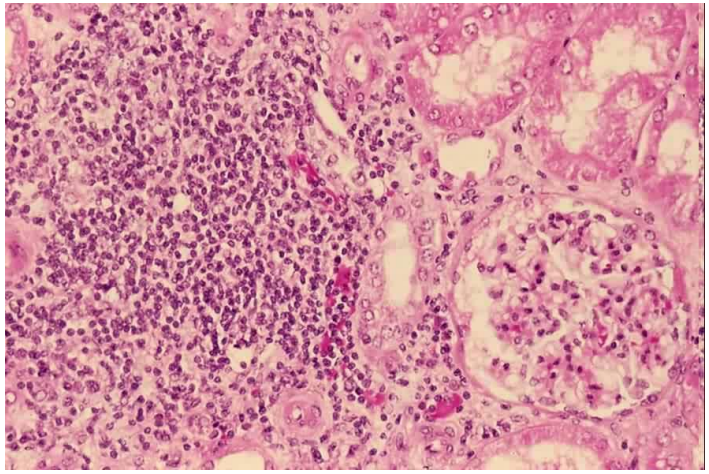
Fig. 5.33 Acute antibody-mediated (humoral) rejection. (A) Graft damage caused by antibody deposition in vessels. (B) Light micrograph showing inflammation (capillaritis) in peritubular capillaries *(arrows)* in a kidney graft. (C) Immunoperoxidase stain shows C4d deposition in peritubular capillaries and a glomerulus. *(Courtesy of Dr. Zoltan Laszik, Department of Pathology, University of California, San Francisco, California.)*

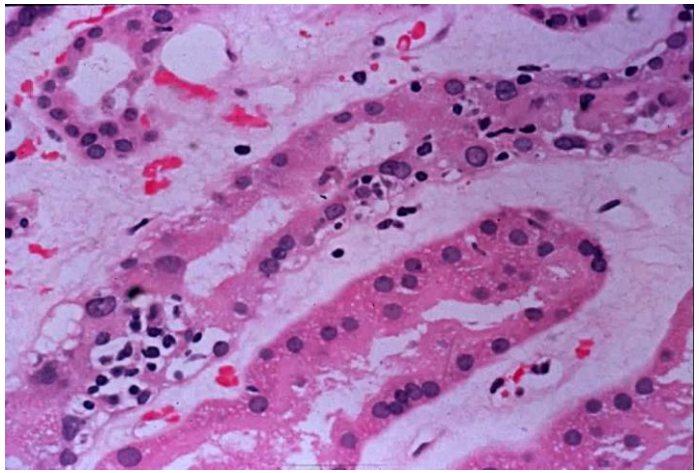
MORPHOLOGY

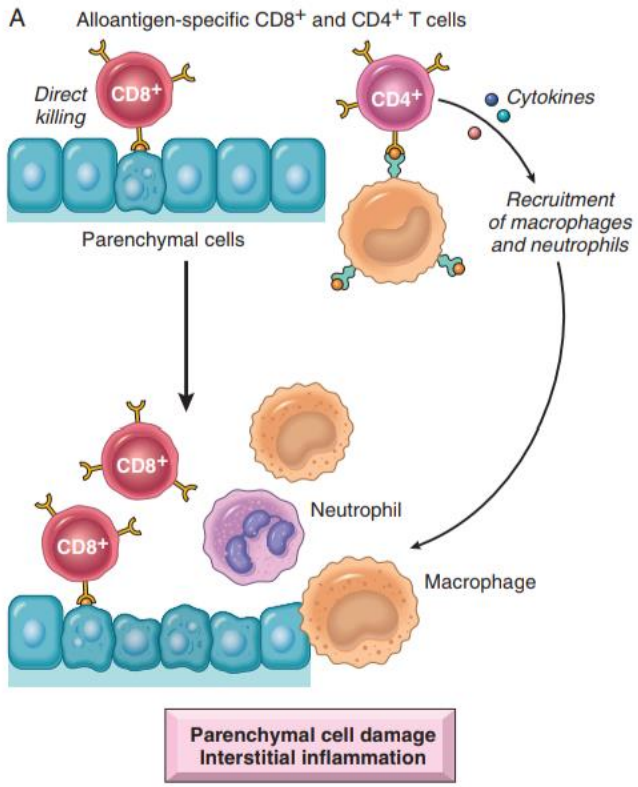
Acute antibody-mediated rejection is manifested mainly by damage to glomeruli and small blood vessels. Typically, there is inflammation of glomeruli and peritubular capillaries (Fig. 5.33B) associated with deposition of complement products, which is due to activation of the complement system by the antibody-dependent classical pathway (Fig. 5.33C). Small vessels also may show focal thrombosis.

Acute Cellular Rejection

- Cell mediated
- Lymphocytic infiltrate of the interstitium and tubulitis (T cells of both types – CD4 & CD8)
- Increased expression of $IL2_R$
- Responds well to therapy







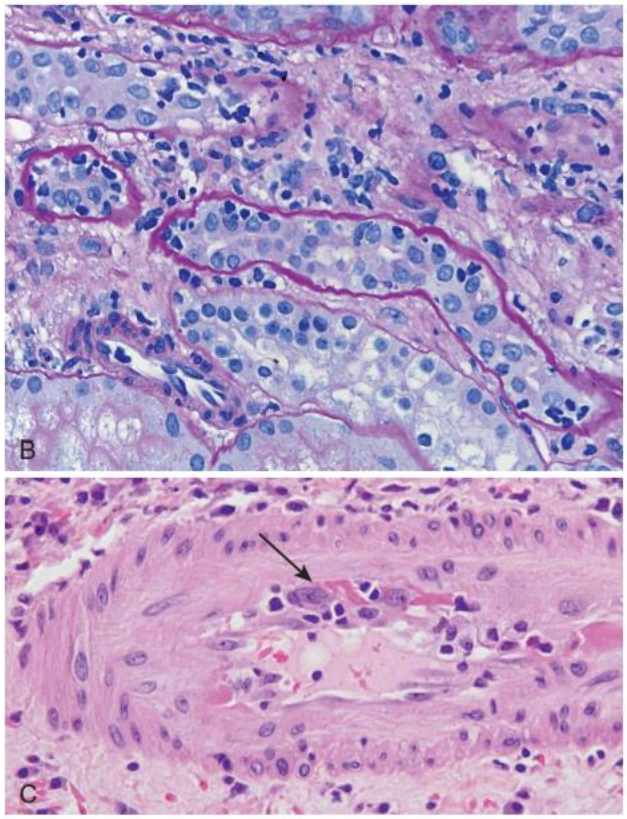


Fig. 5.32 Acute cellular rejection. (A) Destruction of graft cells by T cells. Acute T cell–mediated rejection involves direct killing of graft cells by CD8+ CTLs and inflammation caused by cytokines produced by CD4 T cells. (B) Acute cellular rejection of a kidney graft, manifested by inflammatory cells in the interstitium and between epithelial cells of the tubules (tubulitis). Collapsed tubules are outlined by wavy basement membranes. (C) Rejection vasculitis in a kidney graft. An arteriole is shown with inflammatory cells attacking and undermining the endothelium (endotheliitis) *(arrow). (Courtesy of Drs. Zoltan Laszik and*

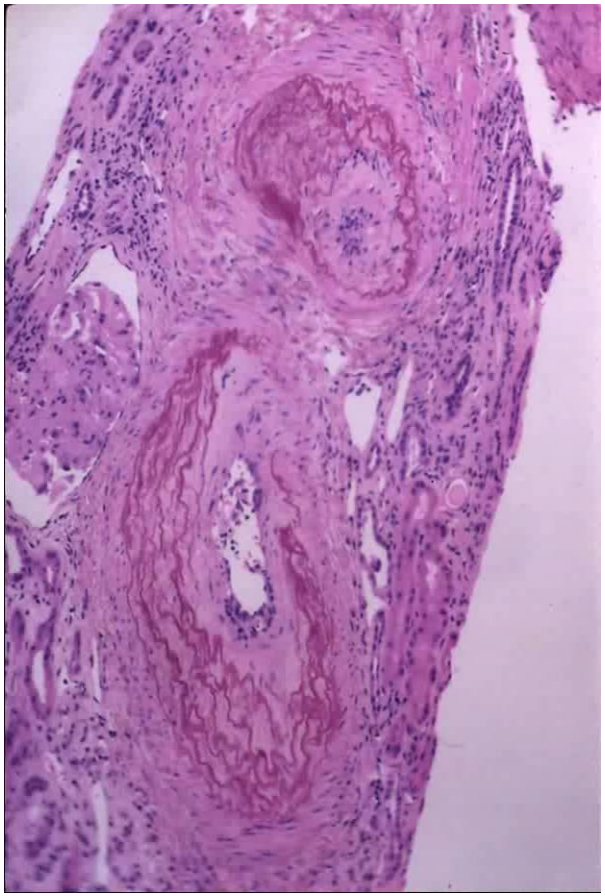
MORPHOLOGY

Acute cellular (T cell-mediated) rejection may produce two different patterns of injury.

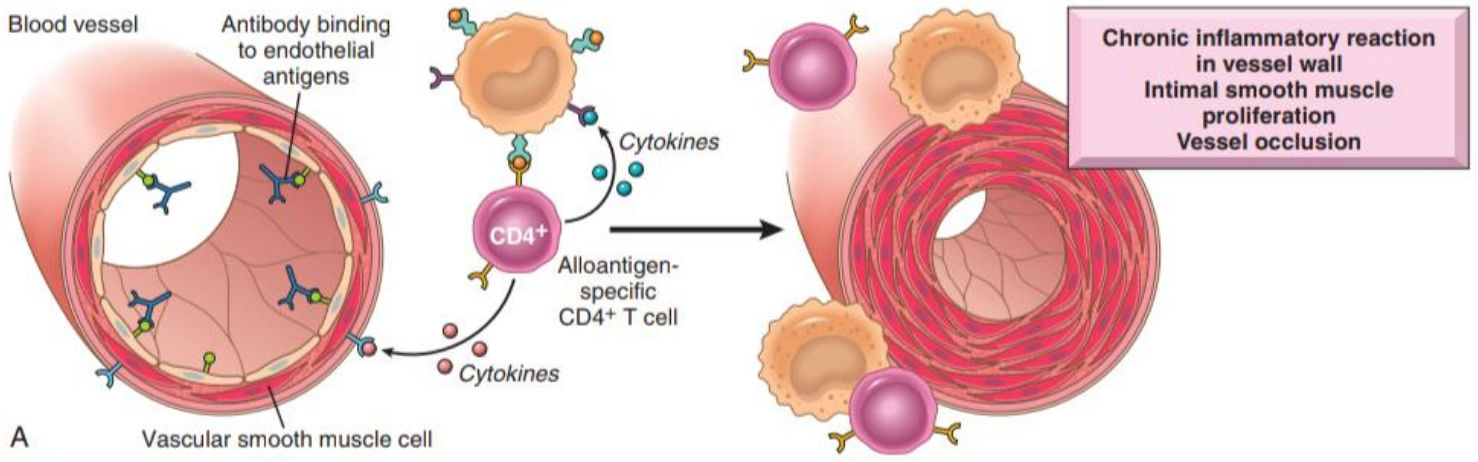
- In the *tubulointerstitial pattern* (sometimes called type I), there is extensive interstitial inflammation and tubular inflammation (tubulitis) associated with focal tubular injury (Fig. 5.32B). As might be expected, the inflammatory infiltrates contain activated CD4+ and CD8+ T lymphocytes.
- The *vascular pattern* shows inflammation of vessels (type II) (Fig. 5.32C) and sometimes necrosis of vessel walls (type III). The affected vessels have swollen endothelial cells, and at places lymphocytes are seen between the endothelium and the vessel wall, a finding termed *endotheliitis* or *intimal arteritis*. The recognition of cellular rejection is important because, in the absence of accompanying humoral rejection, most patients respond well to immunosuppressive therapy.

Chronic Rejection

- Progressive rise in creatinine over 4-6 months
- Vascular changes
  - Intimal fibrosis
  - Progressive luminal narrowing
- Interstitial fibrosis and tubular atrophy
- Ischemic glomerulosclerosis
- No effective therapy



Chronic Rejection



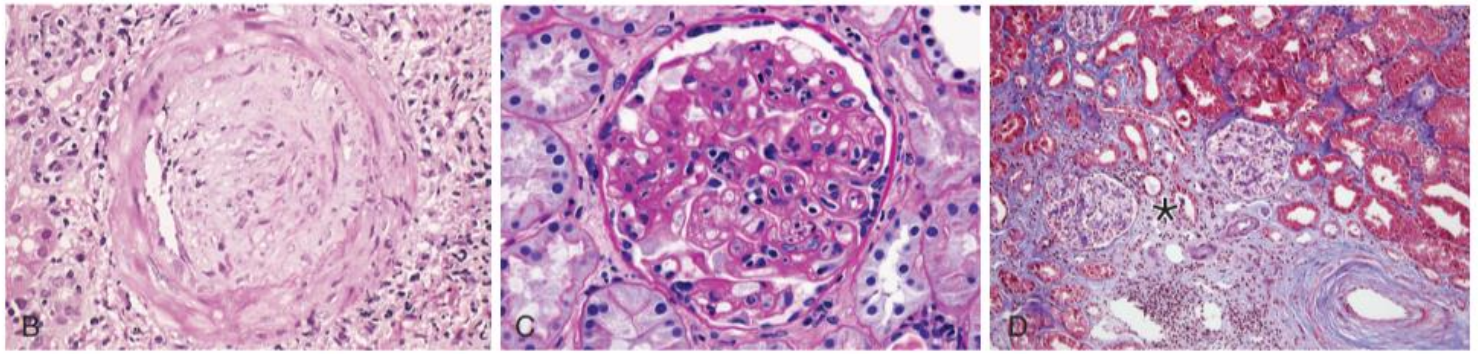


Fig. 5.34 Chronic rejection. (A) Graft arteriosclerosis caused by T-cell cytokines and antibody deposition. (B) Graft arteriosclerosis in a cardiac transplant. (C) Transplant glomerulopathy, the characteristic manifestation of chronic antibody-mediated rejection in the kidney. The glomerulus shows inflammatory cells within the capillary loops (glomerulitis), accumulation of mesangial matrix, and duplication of the capillary basement membrane. (D) Interstitial fibrosis and tubular atrophy, resulting from arteriosclerosis of arteries and arterioles in a chronically rejecting kidney allograft. In this trichrome stain, the blue area *(asterisk)* shows fibrosis, contrasted with the normal kidney *(top right)*. An artery showing prominent arteriosclerosis is shown *(bottom right)*. (***B,*** *Courtesy of Dr. Richard Mitchell, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts. C and D, Courtesy of Dr. Zoltan Laszik, Department of Pathology, University*

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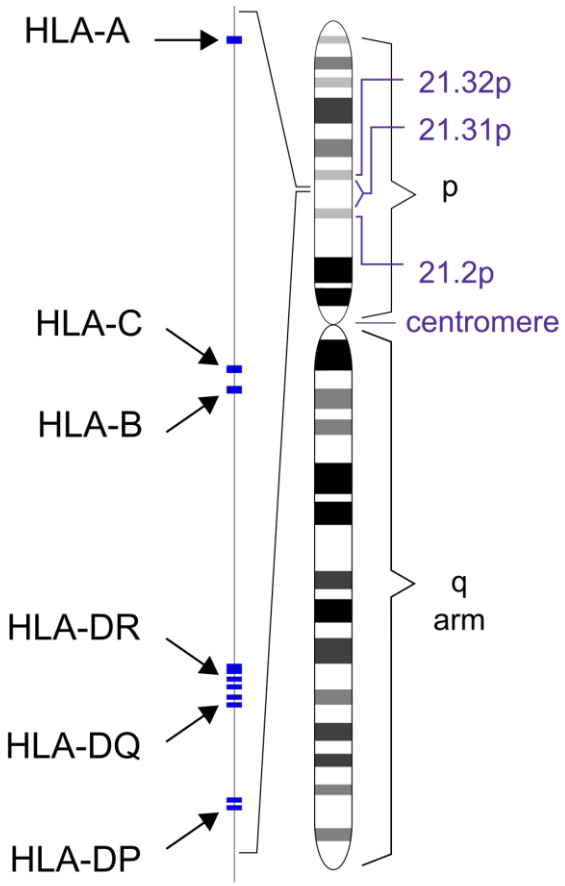
Chronic rejection is dominated by vascular changes, often with intimal thickening and vascular occlusion (Fig. 5.34B). Chronically rejecting kidney grafts show glomerulopathy, with duplication of the basement membrane, likely secondary to chronic endothelial injury (Fig. 5.34C) and peritubular capillaritis with multilayering of peritubular capillary basement membranes. Interstitial fibrosis and tubular atrophy with loss of renal parenchyma may occur secondary to the vascular lesions (Fig. 5.34D). Interstitial mononuclear cell infiltrates are typically sparse.

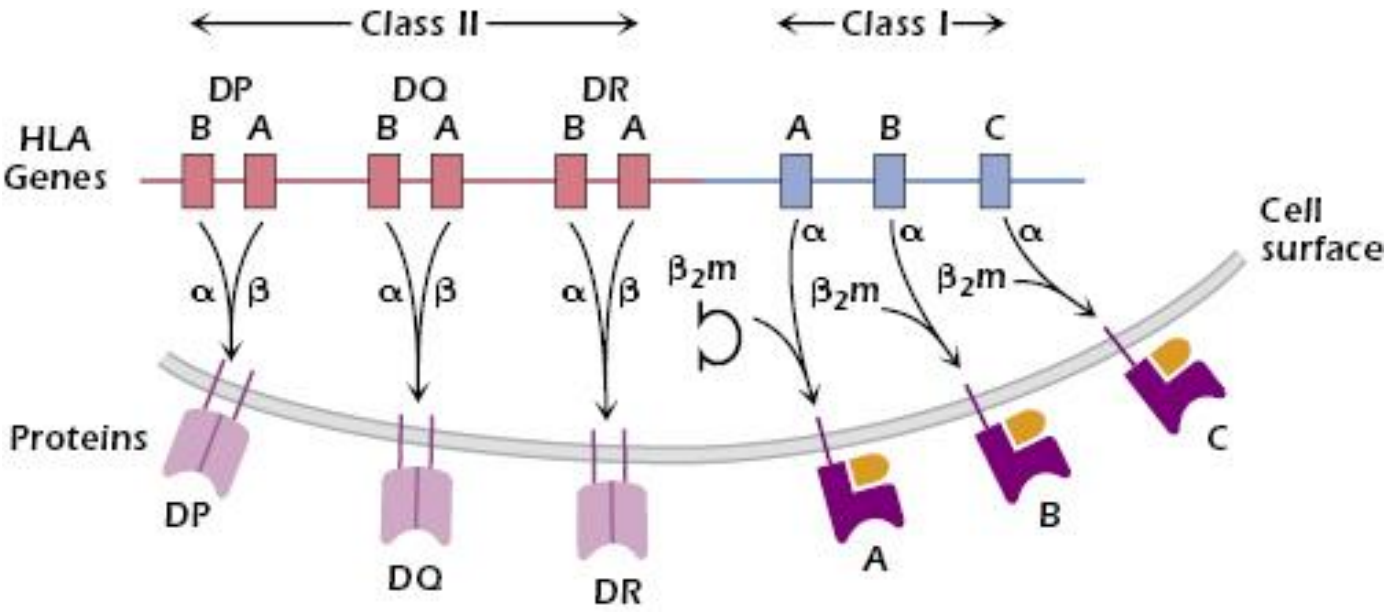
Methods of Increasing Graft Survival

- **HLA matching**
  - Class I for live related
  - Also class II for cadaver transplants
- **Immunosuppression of the recipient**
  - Cyclosporine, Azathioprine, Steroids, Rapamycin & mofetil
  - Blockade of the co-stimulators (CD 80 & CD 40) by immunotherapy (CTLA4Ig)

HLA
MHC Complex



human chromosome 6


Class II
Class I
DP
DQ
DR
B A
B A
B A
A B C
HLA Genes
α β
α β
α β
α
α
α
β2m
β2m
β2m
Cell surface
Proteins
DP
DQ
DR
A
B
C

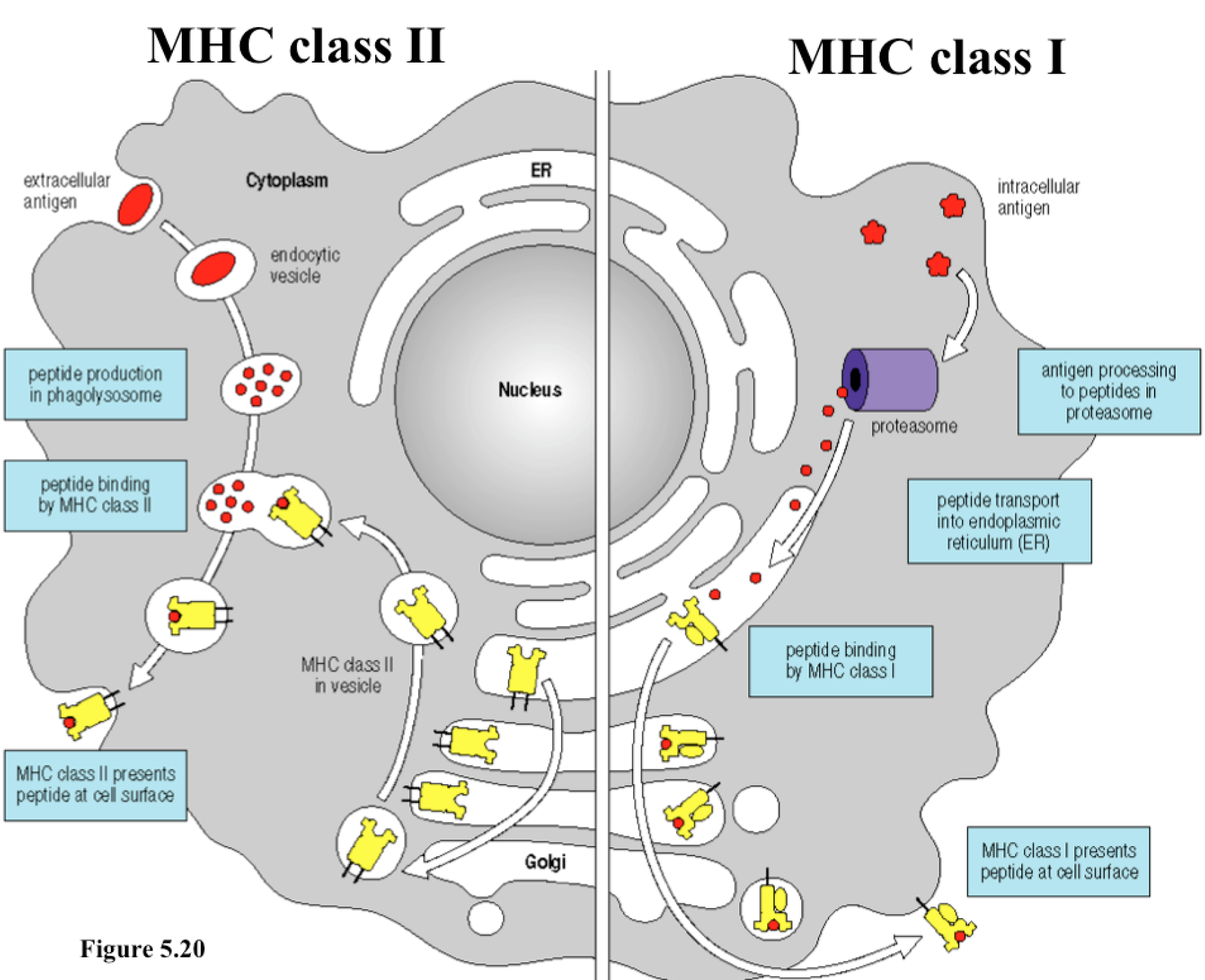

MHC class II
MHC class I
extracellular antigen
Cytoplasm
ER
endocytic vesicle
intracellular antigen
peptide production in phagolysosome
Nucleus
proteasome
antigen processing to peptides in proteasome
peptide binding by MHC class II
peptide transport into endoplasmic reticulum (ER)
peptide binding by MHC class I
MHC class II in vesicle
MHC class II presents peptide at cell surface
Golgi
MHC class I presents peptide at cell surface

Figure 5.20

Transplantation of Other Solid Organs

- Liver
- Heart
  - No HLA matching is usually done
- Lungs
- Pancreas
- Small intestine

Bone Marrow Transplant

- Hematopoietic malignancies
- Aplastic anemia
- Immunodeficiency states
- Certain non-hematopoietic malignancies

Complications of Allogeneic BM Transplants

- Graft versus Host Disease
- Rejection of allogeneic marrow cells
- Immunodeficiency due to myeloablation

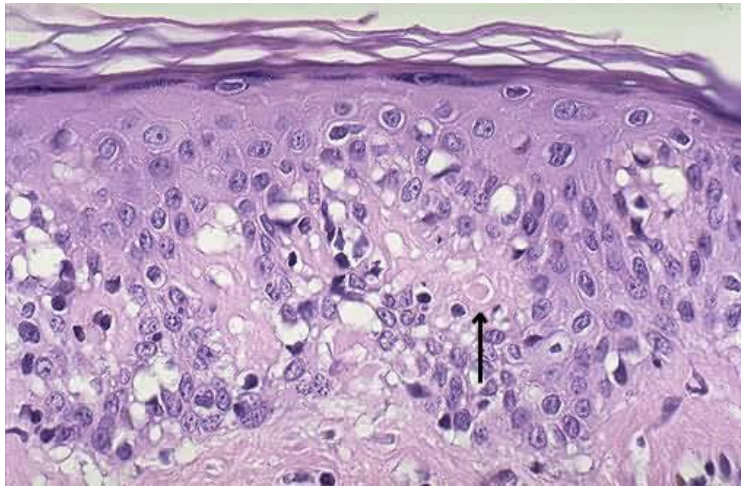
Graft vs. host (GVH) reactions

- Occurs primarily in bone marrow transplantation, because immunologically active cells are given to generally immune ablated host
- May also occur in immune deficient patients given blood transfusions containing HLA-incompatible lymphocytes
- Treated with immunosuppressive drugs such as cyclosporine (inhibits IL-2 formation) or anti – thymocyte globulin (anti-CD3)
- Depletion of donor T cells eliminates GVH

GVH disease

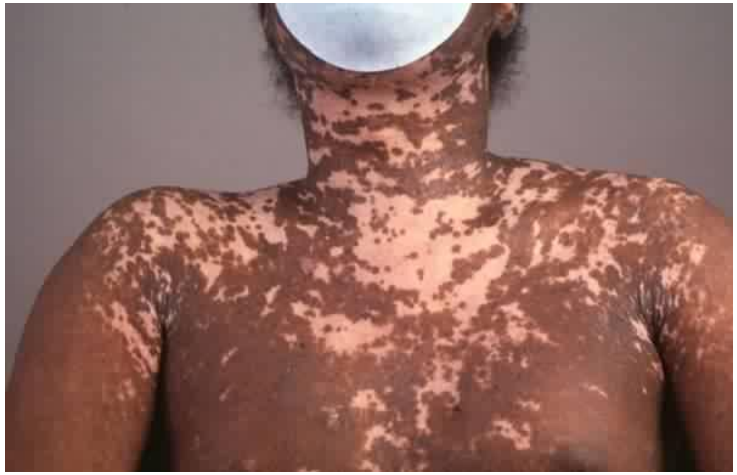
Acute

- Within days to weeks
- Skin, liver & intestine are affected
- Generalized rash with desquamation, jaundice, diarrhoea
- CMV infection – sometimes fatal



Chronic

- May follow acute or may begin insidiously
- Changes may resemble scleroderma



Acute Graft versus Host Disease

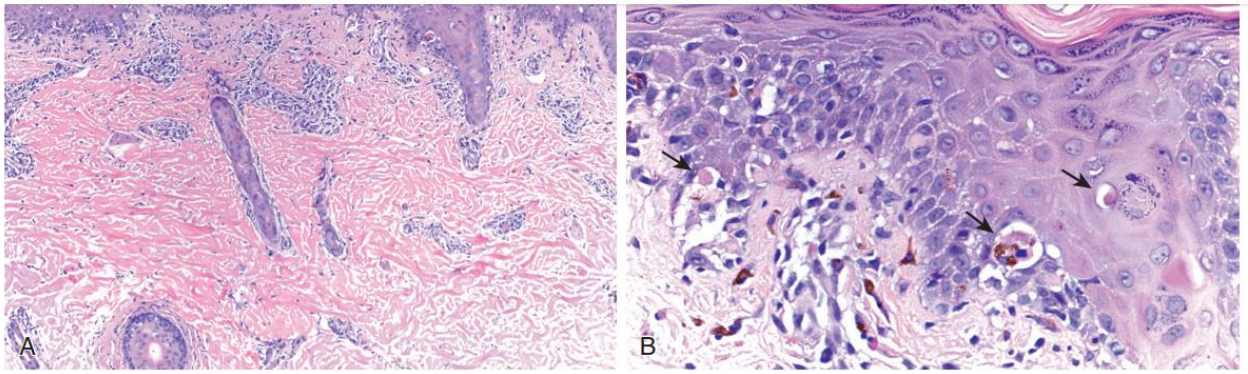


Fig. 5.35 Acute graft-versus-host disease (GVHD) involving the skin. (A) Patchy epithelial cell death and dermal infiltrates of mononuclear cells (lymphocyte and macrophages). (B) Focally dead epithelial cells *(arrows)*.

THANK YOU