Pathology of Renal Allograft

APRIL 2020

Reference: Robbins & Cotran Pathology and Rubin's Pathology

Sufia Husain

Associate Professor

Pathology Department

College of Medicine

KSU, Riyadh

Objectives:

- At the end of the lecture the students will be able to:
- Recognize the concept of renal allograft.
- Describe the pathology of rejection and differentiate acute cell-mediated and antibody-mediated rejection.
- Differentiate between acute and chronic rejection.
- Recognize the pathology of the principal infections inherent to renal transplantation.
- Recognize the pathology of acute and chronic drug toxicity.

Key Outlines:

- Acute T-cell mediated rejection.
- Acute antibody-mediated rejection.
- Pathology of chronic rejection.
- Pathology of the principal infections of the renal allograft.
- Pathology of acute and chronic drug toxicity.

Lecture outline

Pathology of injury in kidney transplant

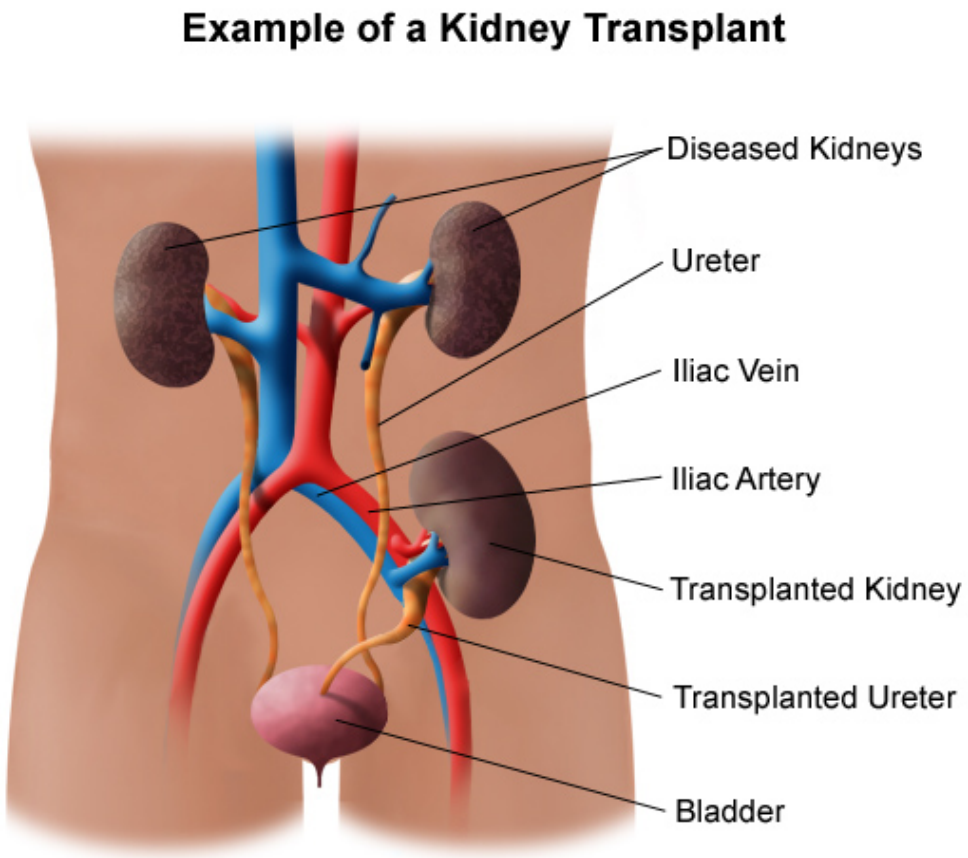
- Harvest injury
- Rejection: hyper-acute rejection, acute rejection (T-cell mediated and antibody mediated) and chronic rejection
- Infections in the renal allograft.
- Drug toxicity, acute and chronic.
- Recurrence of primary disease
- De-novo (new) disease

Kidney transplant:

- End-stage renal disease (resulting from any cause) is treated by renal replacement therapy (e.g. hemofiltration, hemodialysis, peritoneal dialysis) or renal transplant.
- Kidney transplantation is now a routine procedure in most large hospitals in the world.
- The first kidney transplant between humans was conducted in 1933 by a Russian surgeon in Ukraine. The kidney was implanted in the groin under local anesthesia and the host survived four days.
- The patient who donates the kidney is called as the **“donor”.**
- The patient who receives the “new” transplant kidney is called as the **“recipient”.**
- The transplanted (“new”) kidney is called **“donor kidney”, “allograft” or “graft”.**
- The antigens present in the allograft kidney are called **“alloantigens”.**
- The antibodies that are against alloantigens (that target the alloantigens) are anti-allograft antibodies and they are called **“alloantibodies”.**

Kidney transplant

- The donor kidney is placed in the recipients iliac fossa or groin region. The donor ureter is inserted into the bladder. The blood vessels are anastomosed.
- The donor of the kidney can be from a living or a deceased person.



Pathology of injury in kidney transplant

- **Harvest injury**
- Rejection: hyper-acute rejection, acute rejection (T-cell mediated and antibody mediated) and chronic rejection
- Infections in the renal allograft.
- Drug toxicity, acute and chronic.
- Recurrence of primary disease
- De-novo (new) disease

HARVEST INJURY

HARVEST INJURY

- At the time of transplant there can be tubular injury to the transplanted allograft kidney.
- It is generally due to cold ischemia time or the mode of death of the donor.
- It can lead to non-functioning kidney immediately after transplant (the patient develops anuria).
- The good thing is that harvest kidney usually recover with appropriate management.

Pathology of injury in kidney transplant

- Harvest injury
- **Rejection: hyper-acute rejection, acute rejection (T-cell mediated and antibody mediated) and chronic rejection**
- Infections in the renal allograft.
- Drug toxicity, acute and chronic.
- Recurrence of primary disease
- De-novo (new) disease

REJECTION

REJECTION

- Rejection is a major complication seen post-transplantation.
- Transplant rejection occurs when transplanted tissue is rejected by the recipient's immune system and the recipient's immune system destroys the transplanted tissue.

There are different types of rejection:

a) Hyper-acute rejection
b) Acute rejection
   - acute T-cell mediated rejection
   - and acute antibody-mediated rejection.
c) Chronic rejection
   - chronic T-cell mediated rejection
   - and chronic antibody-mediated rejection.

Rejection has been classified by a system called as the Banff Classification

a) HYPERACUTE REJECTION

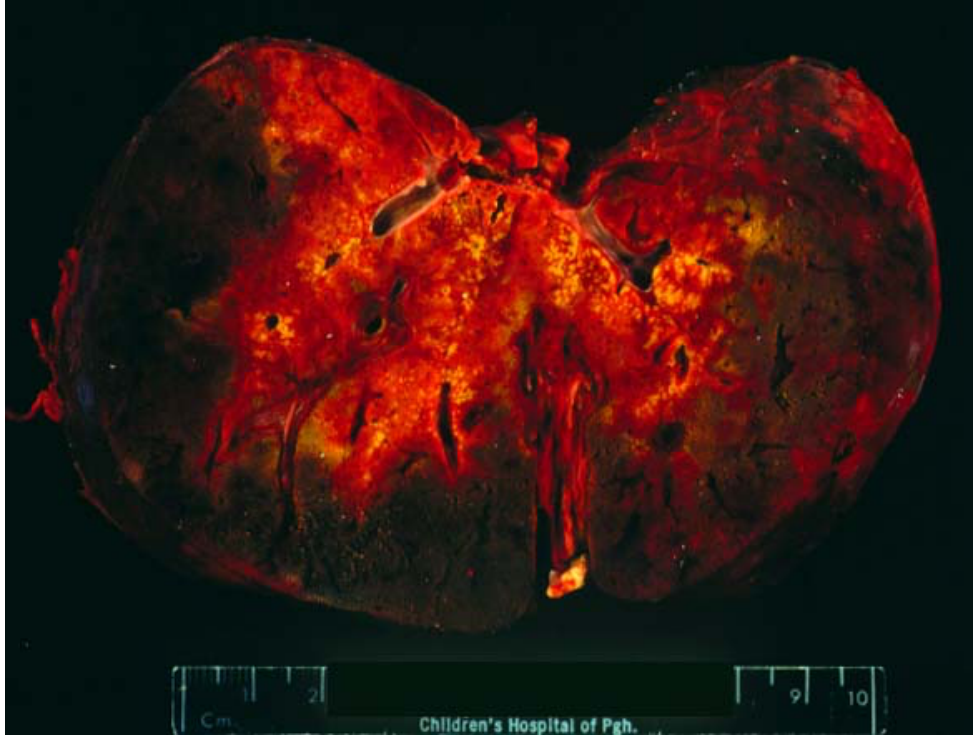
- Rare
- It is rejection of the allograft occurring immediately after implantation and perfusion of graft.
- Occurs within minutes to hours after transplantation.

Gross

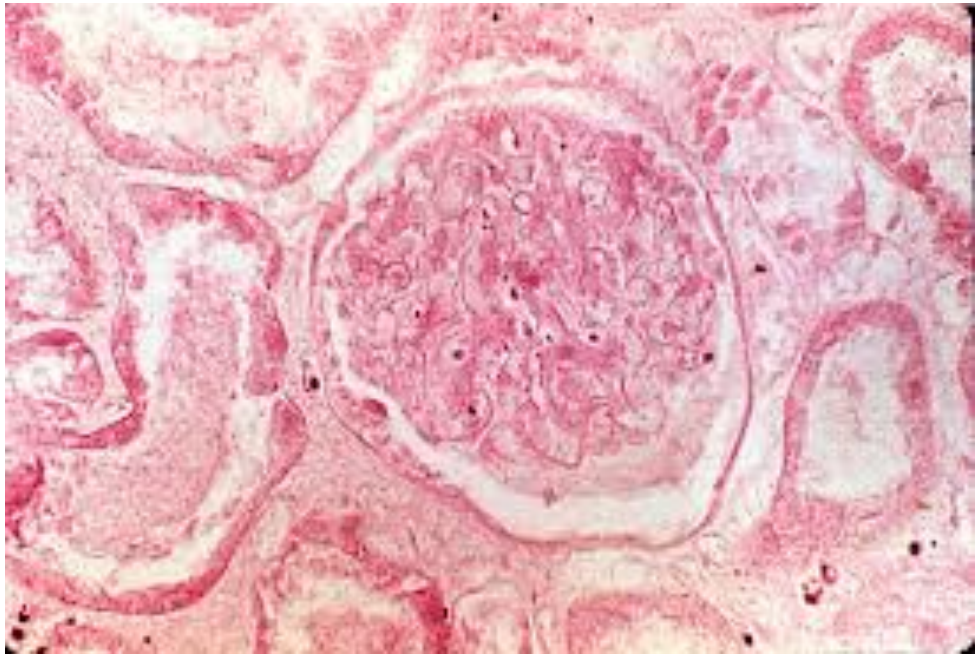
- Cyanosis of graft minutes to hours after perfusion
- Graft becomes swollen, hemorrhagic, and necrotic

Microscopic

- Vasculitis, thrombosis, fibrinoid necrosis of blood vessels
- Thrombi in glomeruli
- Interstitial edema and hemorrhage
- Infarct of the kidney (coagulative necrosis) and loss of graft.



https://tpis.upmc.com/tpis/images/H00021k.jpg



b) ACUTE REJECTION

- Acute Rejection is the most common type of rejection in the newly transplanted kidney patient. It can occur within days or the first few months after surgery. Sometimes it can occur after years.
- 2 types
  - **Acute T-cell mediated rejection/ acute cellular rejection.**
  - **Acute antibody-mediated rejection**.

b) ACUTE REJECTION

Acute T-cell mediated rejection (acute TCMR)

- It is a common form of rejection. It is an acute immune reaction by the recipient against the antigens present in the allograft (called alloantigens). It is mediated by T cells.
- Classically it develops in the first 3 months after transplantation, but may erupt at any time, even after many years.
- Clinically → there is loss of graft function and it presents as rising creatinine.
- In acute TCMR there is infiltration of allograft by lymphocytes (mainly T-cells) and other inflammatory cells. The inflammation is primarily in the tubules (tubulitis) and the interstitium (together called tubulointerstitial inflammation) and may also involve the arteries called vasculitis/arteritis (+/- fibrinoid necrosis of arteries).
- Acute TCMR responds well to immunosuppressive drug therapy.

b) ACUTE REJECTION

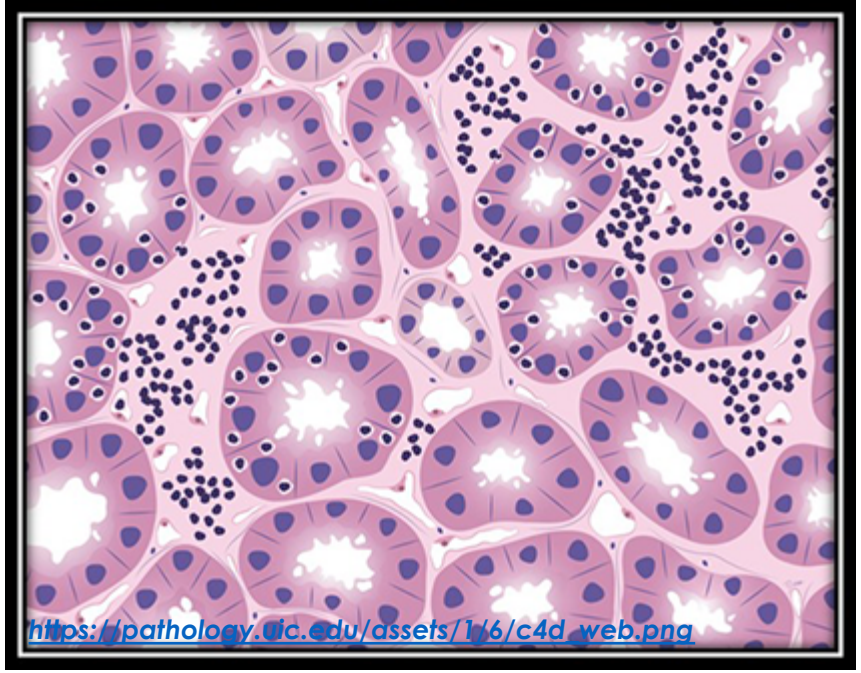
Acute T-cell mediated rejection.

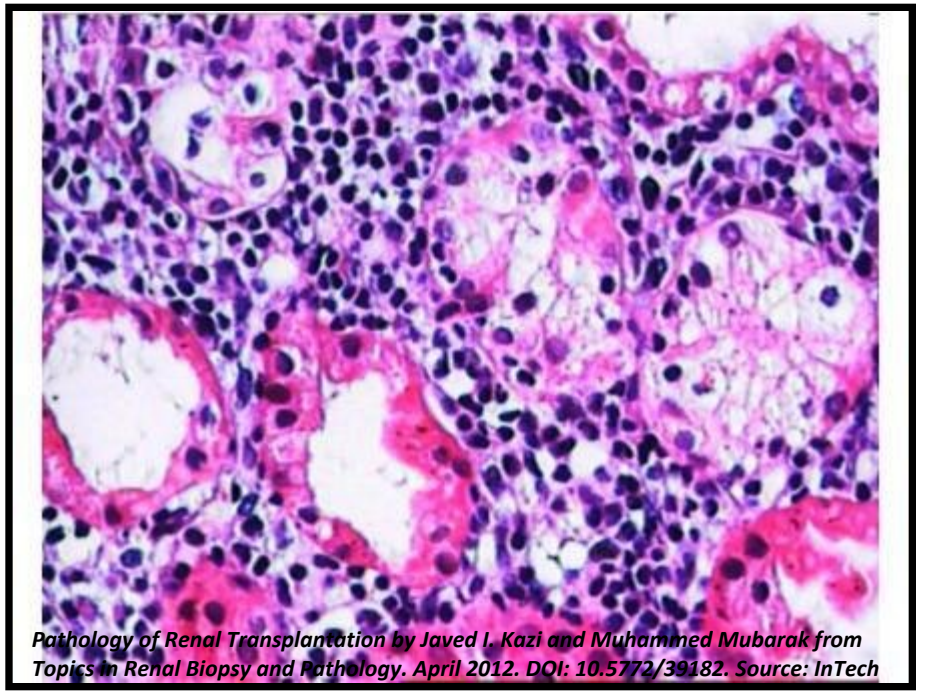
MICROSCOPY

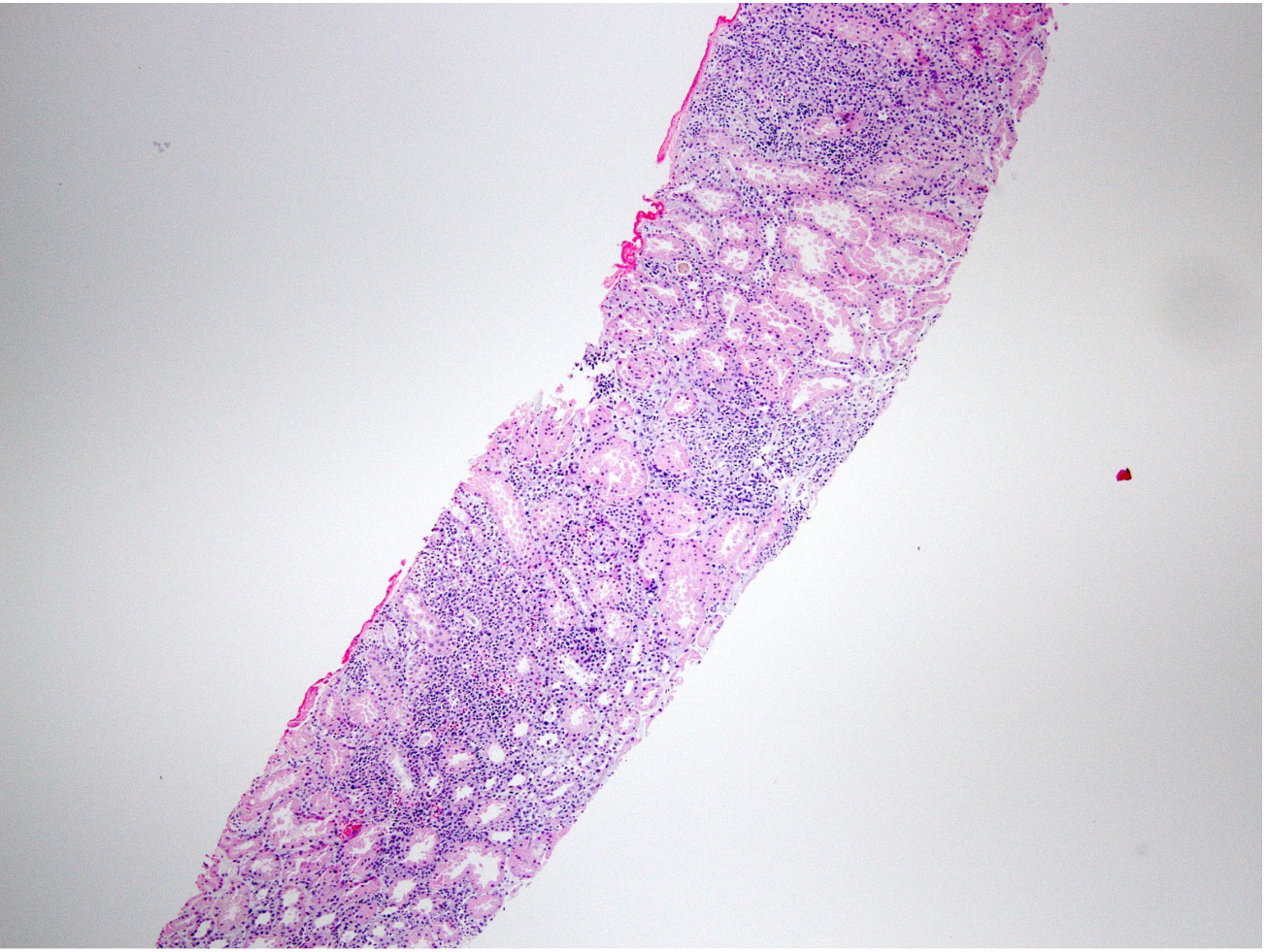
1. **Tubulointerstitial inflammation** with or without **arteritis**

2. **Interstitial edema and sometimes hemorrhage**

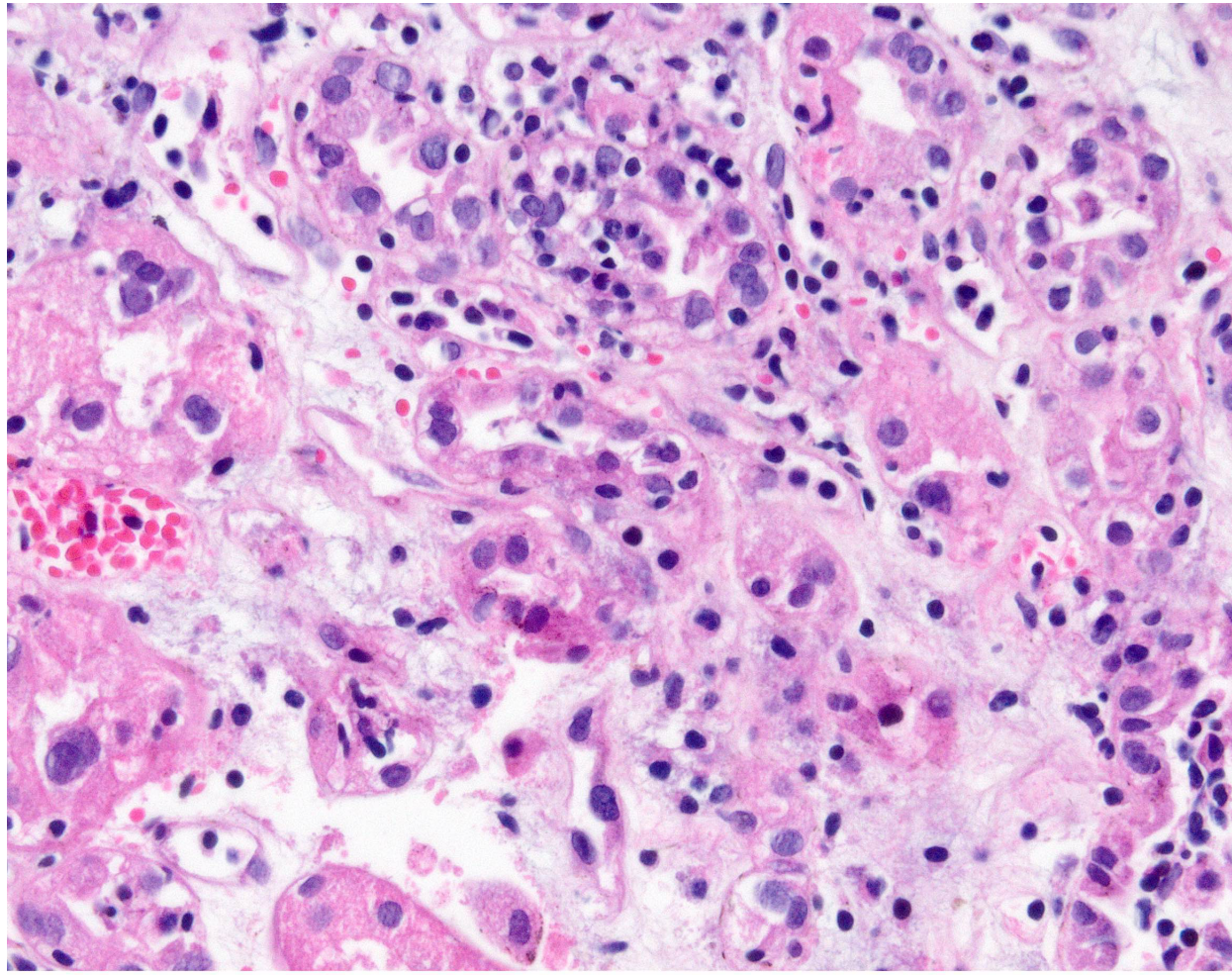
Note: glomerular usually not involved


https://pathology.uic.edu/assets/176/c4d_web.png


Pathology of Renal Transplantation by Javed I. Kazi and Muhammed Mubarak from Topics in Renal Biopsy and Pathology. April 2012. DOI: 10.5772/39182. Source: InTech



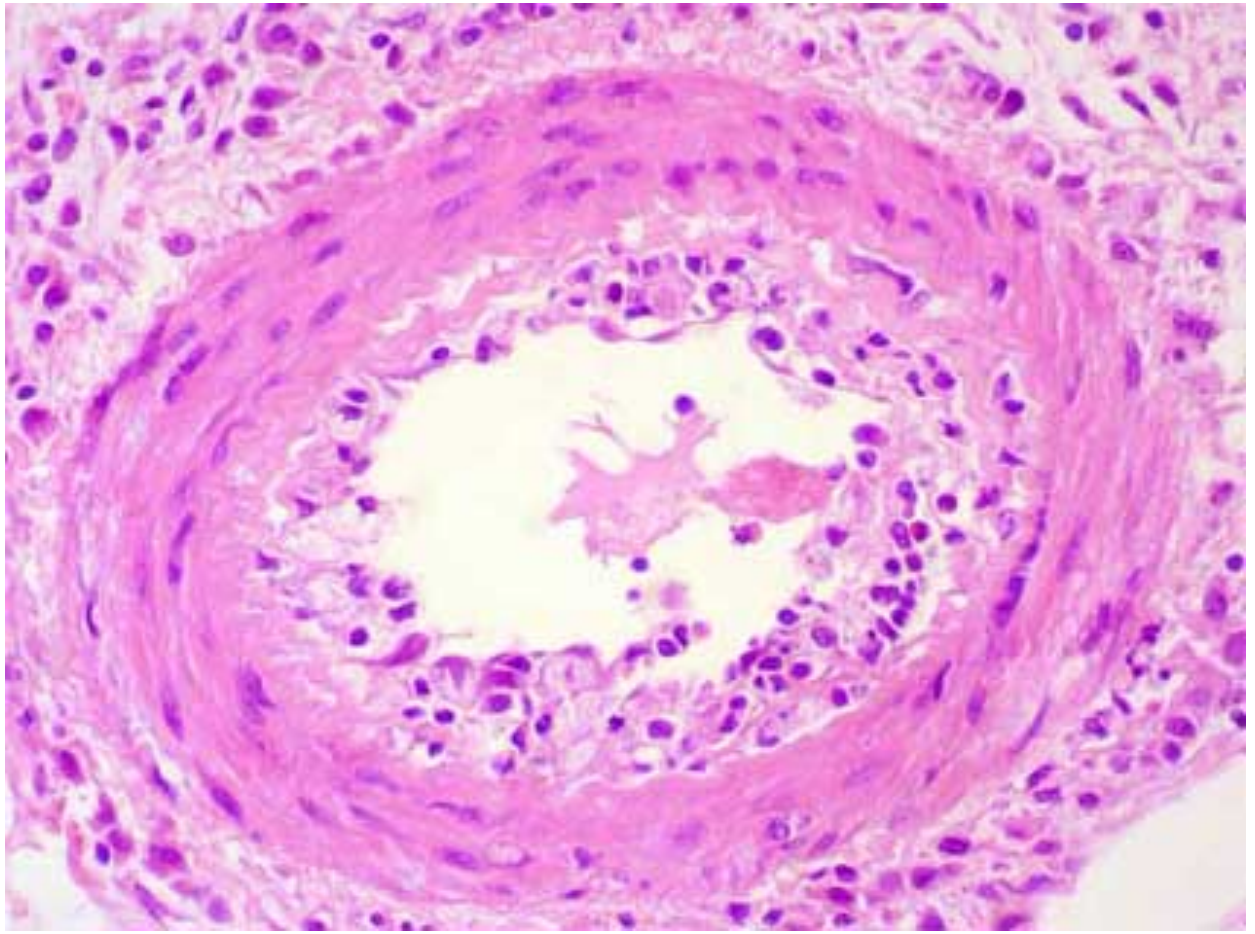
Low power demonstrates prominent inflammatory infiltrate in the tubulointerstitial space



Areas of tubulitis; note inflammatory cells within tubuli

http://www.pathologyoutlines.com/imgau/kidneyacutechroniccellularrejectionsaglam9032_2 and 8973.jpg

ARTERITIS (vasculitis)



https://www.kidneypathology.com/Imagenes/Rechazo/V2.w.jpg

A) ACUTE REJECTION

Acute antibody-mediated rejection (acute ABMR)

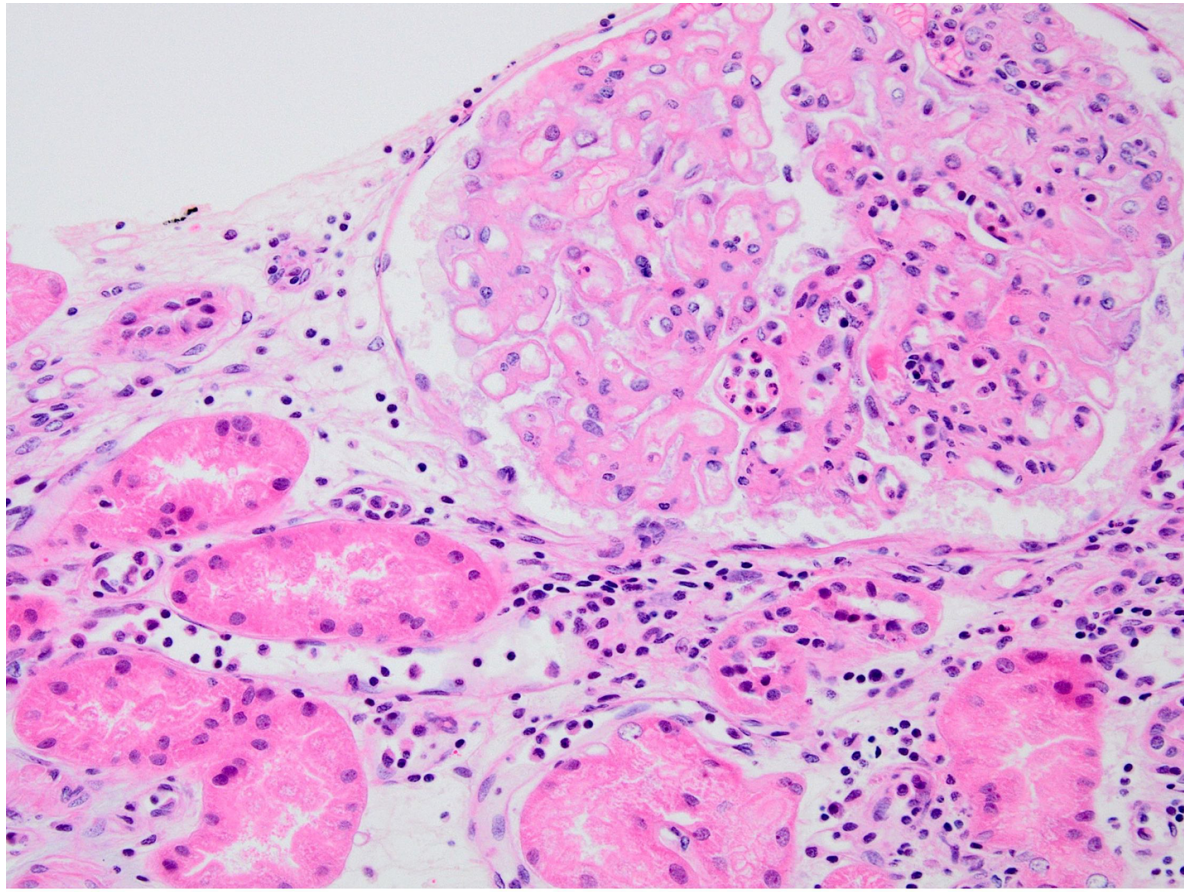
- Also called as acute humoral rejection.
- It is an acute antibody mediated immune reaction.
- It is mediated by the anti-allograft antibodies (alloantibodies) called donor specific antibodies (DSA).
- In it the recipient already has preformed (i.e. present before transplantation) circulating anti-donor specific antibodies (DSA). These antibodies are directed against the endothelial cells in the allograft kidney → they attack the allograft endothelial cells in the blood vessels (esp. the endothelial cells of the glomeruli and peritubular capillaries) → resulting in rejection.
- The microvasculature of the kidney (i.e. glomeruli and peritubular capillaries) is the main target.
- Clinically there is loss of graft function presenting as rising creatinine.

Acute rejection

Acute antibody-mediated rejection (acute ABMR)

- Microscopy:
  - ✓ Glomerulitis, capillaritis of the peritubular capillaries (peritubular capillaritis).
  - ✓ Positive C4d immunostain in the peritubular capillaries.
  - ✓ Acute tubular injury/ necrosis.
  - ✓ Arteritis +/- fibrinoid necrosis.
  - ✓ Acute thrombotic microangiopathy like picture

NOTE: arteritis/ vasculitis can be seen in both acute TCMR and acute ABMR.



Glomerulitis & peritubular capillaritis

c) CHRONIC REJECTION

- Chronic rejection is the type of rejection that happens over an extended period of time and can eventually lead to loss of the graft.
- Usually occurs after the first year of transplantation.
- Persistent or recurrent episodes of TCMR or ABMR → lead to chronic changes in allograft → chronic rejection (chronic TCMR and chronic ABMR) → end stage allograft kidney (graft loss).
- Clinically: gradual rise in serum creatinine. Patients presents with chronic graft dysfunction/ chronic renal failure, proteinuria and hypertension.
- It does not respond to immunosuppressive therapy.
- Additional information → Microscopy can show any or all of the following
  - ✓ Tubulitis and tubular atrophy.
  - ✓ Interstitial inflammation and fibrosis.
  - ✓ Arteries show intimal fibrosis with chronic inflammation called chronic transplant arteriopathy.
  - ✓ Glomeruli: global or focal segmental glomerulosclerosis
  - ✓ Chronic ABMR also shows a unique type of glomerular injury called **transplant glomerulopathy.**

Pathology of injury in kidney transplant

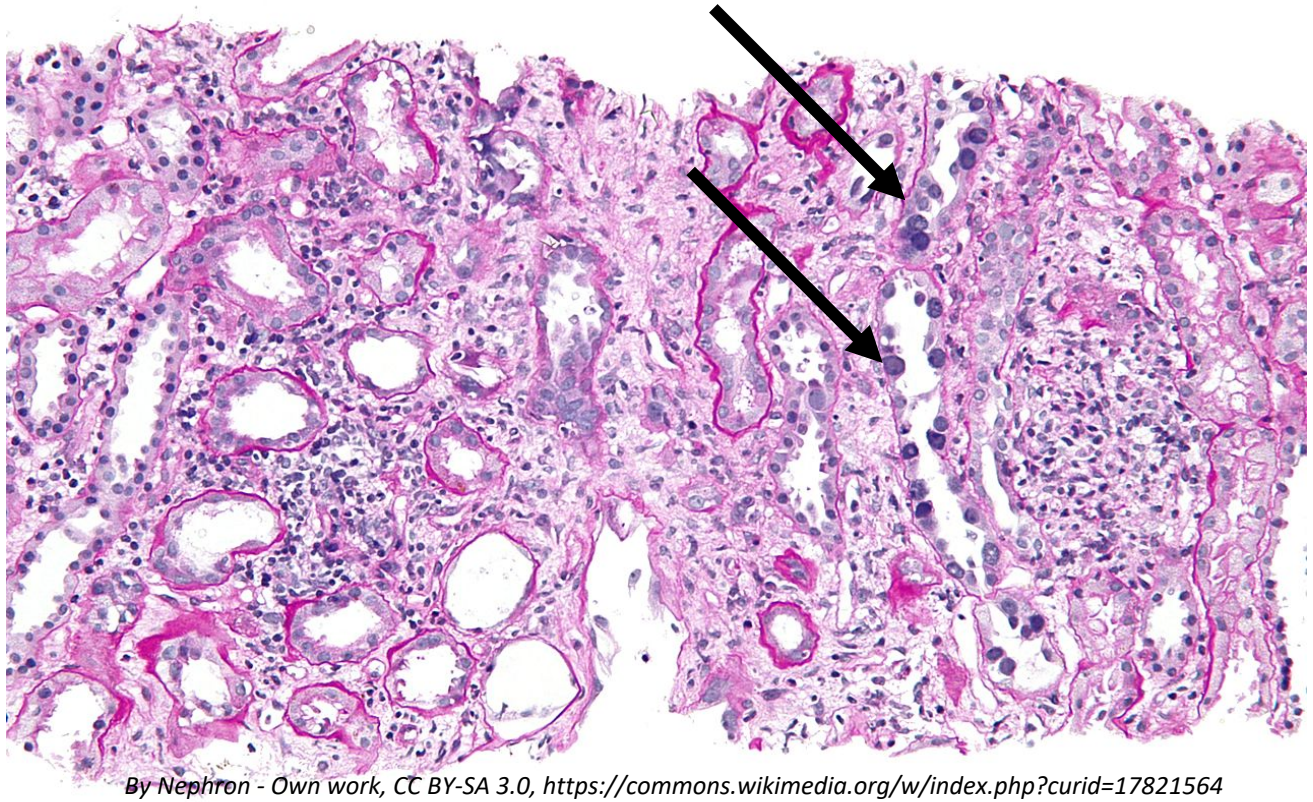
- Harvest injury
- Rejection: hyper-acute rejection, acute rejection (T-cell mediated and antibody mediated) and chronic rejection
- **Infections of the renal allograft.**
- Drug toxicity, acute and chronic.
- Recurrence of primary disease
- De-novo (new) disease

INFECTIONS OF THE RENAL ALLOGRAFT

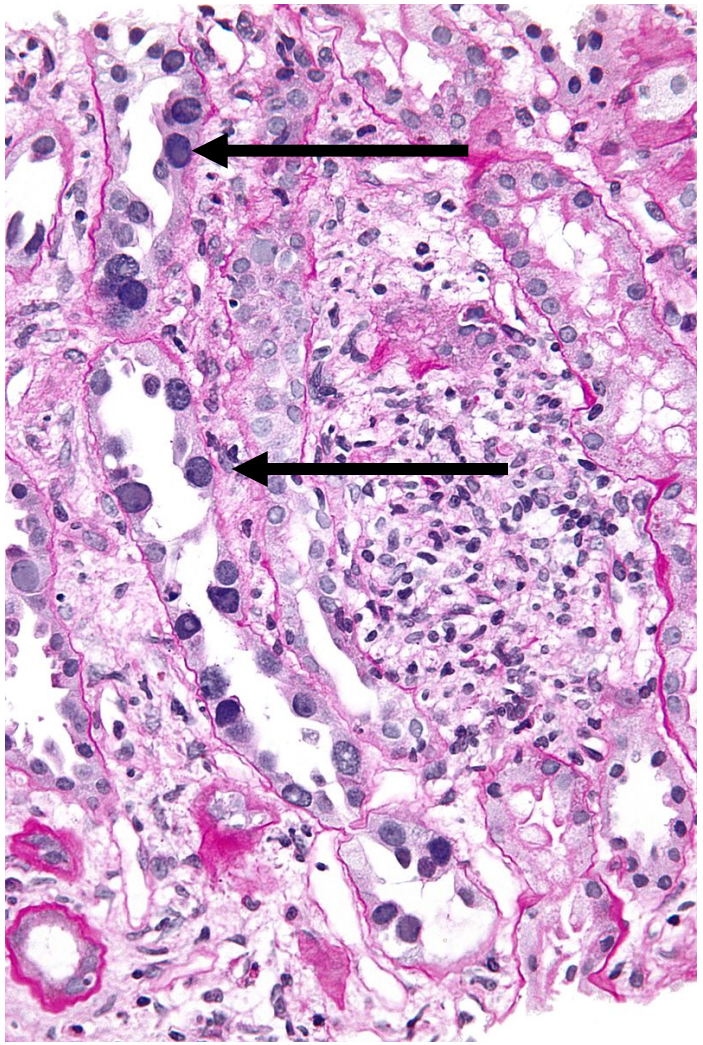
INFECTIONS OF THE RENAL ALLOGRAFT

- The patients who are recipients of allograft kidney are given various immunosuppressive drugs and are therefore immunosuppressed (immunocompromised). This makes such patients predisposed to various renal infections like Polyomavirus (SV40 virus), Adenovirus, Cytomegalovirus and Epstein–Barr virus (EBV).
- They primarily infect the tubules and cause tubulointerstitial inflammation and acute tubular injury. The infected tubular epithelial cells show viral nuclear changes.
- Theses infections can lead to graft loss.
- Infection with EBV can also lead to post transplant lymphoproliferative disorder (PTLD).

Renal tubules showing Polyomavirus infection in allograft kidney (arrows)



By Nephron - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=17821564



Pathology of injury in kidney transplant

- Harvest injury
- Rejection: hyper-acute rejection, acute rejection (T-cell mediated and antibody mediated) and chronic rejection
- Infections of the renal allograft.
- **Drug toxicity, acute and chronic.**
- Recurrence of primary disease
- De-novo (new) disease

DRUG TOXICITY

Drug toxicity

- Calcineurin inhibitors (CNIs) are immunosuppressive drugs given to the recipients in order to decrease the recipients immune system's response to the transplanted kidney and therefore help suppress acute rejection.
- Examples of CNI drugs: cyclosporine and tacrolimus
- The problem is that CNIs are also nephrotoxic and can cause acute or chronic damage to the graft. They can cause acute CNI toxicity and chronic CNI toxicity in the kidney
- Blood tests show:
  - Rising serum creatinine,
  - Elevated levels of CNI in blood

ADDITIONAL information

- **Acute CNI toxicity shows:**
  - acute tubular injury
  - isometric vacuolization of proximal tubules
  - acute thrombotic microangiopathy like picture.
- **Chronic CNI toxicity shows:**
  - striped interstitial fibrosis
  - tubular atrophy
  - Microcalcifications
  - nodular arteriolar hyalinosis
  - chronic thrombotic microangiopathy like picture.

Pathology of injury in kidney transplant

- Harvest injury
- Rejection: hyper-acute rejection, acute rejection (T-cell mediated and antibody mediated) and chronic rejection
- Infections of the renal allograft.
- Drug toxicity, acute and chronic.
- **Recurrence of primary disease**
- **De-novo (new) disease**

RECURRENCE OF PRIMARY DISEASE
AND
DE-NOVO (NEW) DISEASE

RECURRENT & DE-NOVO DISEASE

5) Recurrence of primary disease

- The primary disease which lead to end stage kidney and eventual transplant can recur as early as 6 months post-transplant.

6) De-novo (new) disease/ glomerulonephritis

- It is the development of another kidney disease in the renal allograft, different from the disease the patient originally suffered from.
- It is rare.

END