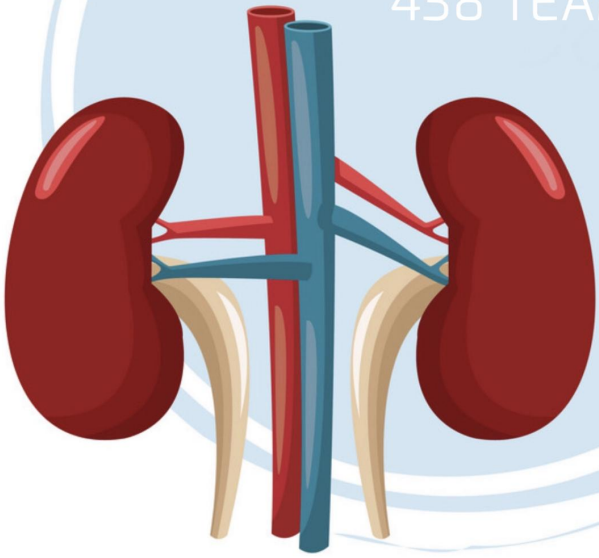
Editing file

Pathology

438 TEAM



PATHOLOGY OF RENAL ALLOGRAFT

Objectives:

- 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.

Color index:

Black: original content.
Red: Important.
Light Purple: From Robbin's.
Blue: only found in boys slides.

Green: Boy's doctor notes .
Dark orange: Girl's Doctor notes.
Grey: Explanation.
Pink: Only found in girls slides.

Pathology

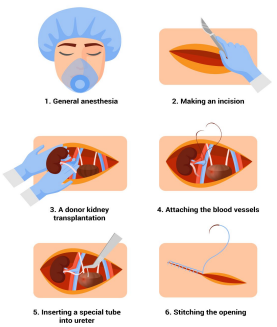
Reviewed by: Rezan AlRabah & Ibrahim AlBaqshi

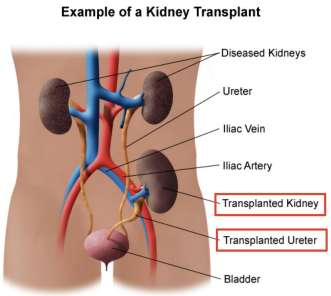
Introduction

Kidney transplant:

- Renal transplantation and dialysis are the treatments for patients with end-stage renal disease (ESRD) resulting from a variety of causes.
- 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 donor kidney which is placed in the recipients iliac fossa or groin region. (usually we do not remove the old kidney, unless it's in risk of infection).
- The ureter is inserted into the bladder.
- The blood vessels are anastomosed.





The donor of the kidney can be living or deceased.

Important terminology:

Word	Definition
Allograft	The transplanted kidney is called the allograft or the graft.
Alloantigen	The antigens present in the allograft kidney

Harvest injury

- At the time of transplant there can be tubular injury to the transplanted allograft kidney.
- It is generally due to cold ischemia (the time between the chilling of the kidney & the time it is warmed) time or the mode of donor death.
- It can lead to non-functioning kidney immediately after engraftment in which the patient will have anuria.
- Harvest kidney usually recover.

Rejection

Definition

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

Rejection has been classified by a system called as the **Banff Classification**.
Types of rejection:

Hyperacute rejection	Acute rejection		Chronic rejection	
-	T-cell mediated rejection	antibody-mediated rejection.	T-cell mediated rejection	antibody-mediated rejection.

A) HYPERACUTE REJECTION (RARE)

Timing

- Rejection **immediately** after implantation and perfusion of graft; Occurs within **minutes** to **hours** after transplantation.
- The transplanted kidney should immediately be taken out.

It leads to

- Haemorrhage
- Loss of graft
- Arterial thrombosis
- Vasculitis
- Infarct of the kidney (coagulative necrosis)
- Oedema
- Fibrinoid necrosis

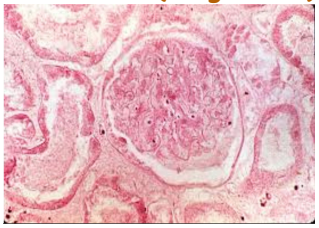
Morphology

Gross

- Cyanosis of graft **minutes** to **hours** after perfusion.
- Becomes **swollen**, **hemorrhagic**, and **necrotic**.

Microscopic

- Thrombi in glomeruli and arterioles.
- Interstitial edema and hemorrhage.
- **Cortical necrosis** (coagulative) in 12-24 hours.



B) Acute rejection

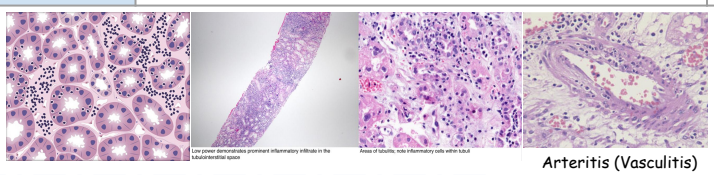
Features

- Acute Rejection is the most common type of rejection in the newly transplanted kidney patient.
- Developing in a short time span. It can occur within **days** or **the first few months after surgery**. Sometimes it can occur after years.

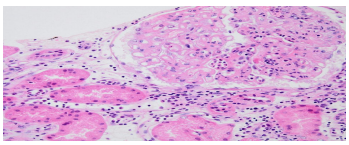
Types of acute rejection

(can be differentiated by biopsy)

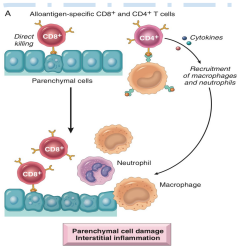
	T-CELL MEDIATED REJECTION (Common form of rejection)	ANTIBODY-MEDIATED REJECTION (Acute humoral rejection)
Definition	It is an acute immune reaction by the recipient against the alloantigens (antigens present in the allograft).	It is an acute immune reaction in which the recipient has preformed circulating anti-donor specific alloantibodies (DSA). These antibodies are directed against the endothelial cells in the allograft → rejection. (ABs formed even before transplant)
Mediated by	**T-Cells.**	**Anti-donor specific antibodies.**
Clinical features	• Loss of graft function. • Rising creatinine. (checked constantly) • It responds well to immunosuppressive drug therapy. • It develops in the first 3 months after transplantation, but may erupt at any time, even after many years.	• Loss of graft function. • Rising creatinine. • Acute renal failure and oliguria. • Oliguria
Characteristics	There is infiltration of allograft by lymphocytes and other inflammatory cells.	The microvasculature of the kidney (i.e. glomeruli and peritubular capillaries) is the main target.
Microscopy	• Interstitial edema and sometimes hemorrhage. • Tubulointerstitial inflammation (interstitial inflammation & tubulitis) • With or without arteritis (+/- fibrinoid necrosis of arteries). Note: glomeruli aren't usually involved.	• Glomerulitis, capillaritis of the peritubular capillaries, C4d stain positivity in the peritubular capillaries. • Acute tubular injury/ necrosis. • Arteritis +/- fibrinoid necrosis. • Acute thrombotic microangiopathy like picture.



Arteritis (Vasculitis)



Glomerulitis and Peritubular capillaritis



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.

C) CHRONIC REJECTION

Features

- Can **lead to loss of the graft**.
- **It does not respond to immunosuppressive therapy**.

Timing — Happens over an extended period of time (Usually occurs after the first year of transplantation).

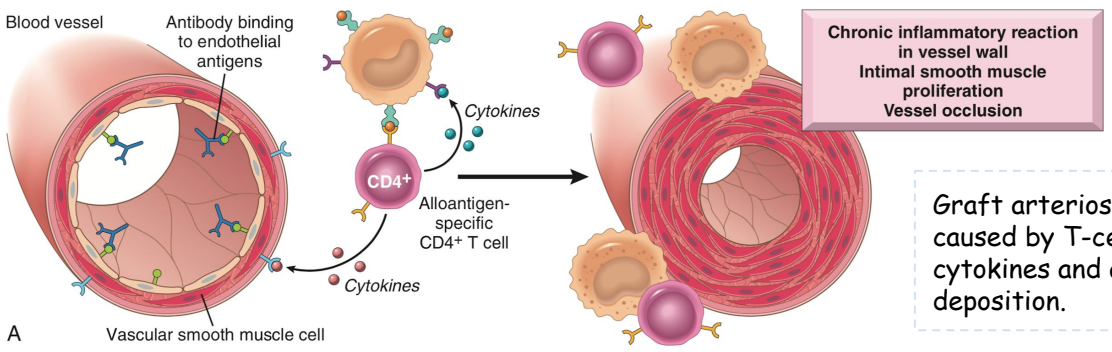
Persistent or recurrent episodes of T-cell-mediated rejection or antibody-mediated rejection → Chronic changes in allograft. → Chronic rejection.

Clinically

- Gradual rise in serum creatinine
- Hypertension
- Patients presents with chronic graft dysfunction/ chronic renal failure
- Proteinuria

Microscopic findings

1. Tubular atrophy.
2. Interstitial fibrosis.
3. Arteries show intimal fibrosis with chronic inflammation.
4. Chronic antibody mediated rejection also shows a unique type of glomerular injury called transplant glomerulopathy.



Graft arteriosclerosis caused by T-cell cytokines and antibody deposition.

INFECTIONS OF THE RENAL ALLOGRAFT

The renal allograft recipient is immunosupressed and predisposed to renal infections like adenovirus, cytomegalovirus and polyomavirus and Epstein-Barr virus (EBV).

They cause mononuclear tubulointerstitial inflammation, acute tubular injury and the tubular epithelial cells show viral cytopathic changes (Ground glass).

Infection with EBV can also lead to post transplant lymphoproliferative disorder (PTLD)[1].

They can lead to graft loss.

Infection -> immunosuppressants needs to be reduced to fight it -> rejection will start. So balance should be found to avoid this vicious cycle.

DRUG TOXICITY

Calcineurin inhibitors/CNIs are immunosuppressive drugs used to decrease the recipients immune system's response to the transplanted kidney and therefore helps suppress acute rejection.
Examples of CNI drugs:

- Cyclosporine
- Tacrolimus

CNIs are also Nephrotoxic and can cause acute or chronic damage to the graft.

Acute CNI toxicity in the kidney	Chronic CNI toxicity in the kidney
Acute tubular injury with focal isometric vacuolization of proximal tubular segments and acute thrombotic microangiopathy.	Chronic CNI toxicity striped interstitial fibrosis and tubular atrophy, microcalcifications, nodular arteriolar hyalinosis and chronic thrombotic microangiopathy.

Lab Results:

- Elevated of serum creatinine.
- Elevated blood/ serum CNI levels.

1- **(PTLD)** are lymphomas that can develop after a transplant. 'Lymphoproliferative' means relating to proliferation (rapid growth) of lymphocytes.

RECURRENT & DE-NOVO DISEASE

Recurrence of primary disease	De-novo (new) disease/ glomerulonephritis
• The primary disease which lead to end stage kidney and eventual transplant can recur as early as 6 months post-transplant. • It is not very common.	• It is the development of another kidney disease in the renal allograft, different from the disease the patient originally suffered from. • It is very rare.

We Are Done!

It has been a crazy journey all through our first year, MED438 batch!

We truly wish that our team helped ease the stress of 1st year pathology.

now, we would like to share with you the names of our amazing team members that made this team what it is throughout this year:

Jehad Alorainy, Nawaf Albhijan, Suhail Basuhail, Khaled Alkhani. Muaath AlJehani. Alwaleed Alarabi, Mohaned Makkawi, Abdulaziz Alghamdi, Faisal Almuhid, Mohammed Alhumud, Alwaleed Alsaleh, Tariq Aloqail, Mohammed Alqahtani, Hani Alhudhaif, Mohammad Aljumah, Abdulla Alhawamdeh, Alhanouf Alhaluli, Amirah Alzahrani, Danah Alhalees, Deana Awartani, Elaf AlMusahel, Ghaida Alshehri, Joud AlJebreen, Lama Alassiri, Lama Alzamil, Leena Alnassar, Leen Almazroa, Njoud Alali, Noura Alturki, Reema Alserhani, Rema Almutawa, Sarah Alarifi, Taiba Alzaid.

Pathology

Summary

Harvest injury

- Tubular injury to the transplanted allograft kidney, due to cold ischemia time or the mode of donor death.
- Usually recover.

Rejection is a major complication seen post-transplantation.
Types of Rejection:

Hyperacute rejection	Acute rejection	Chronic rejection
• **immediately**. • **Minutes** to **hours** after transplantation.	• The most common type of rejection. • **Days** or **the first few months after surgery**. Sometimes it can occur after years.	• Usually occurs after the first year of transplantation. • Lead to loss of the graft. • Doesn't respond to immunosuppressive therapy.

Infection Of The Renal Allograft

- The renal allograft immunosupressed & predisposed to renal infections like adenovirus, cytomegalovirus and polyomavirus and (EBV).
- They can lead to graft loss.

Drug Toxicity

- CNI are immunosuppressive drugs used to decrease the recipients immune system's response to the transplanted kidney and therefore helps suppress acute rejection.
- Examples of CNI drugs: Cyclosporine , Tacrolimus.

Recurrence of primary disease	De-novo (new) disease/ glomerulonephritis
• The primary disease which lead to end stage kidney. • It is not very common.	• It is the development of another kidney disease in the renal allograft. • It is very rare.

Quiz

Answer key: Answers Explanation File!

4) A : 3) E : 2) C : 1) E

1) A 52-year-old woman with a history of systemic hypertension and chronic renal failure undergoes kidney transplantation, but the graft fails to produce urine. A renal biopsy is diagnosed as "hyperacute transplant rejection." Graft rejection in this patient is caused primarily by which of the following mediators of immunity and inflammation?	
A	Cytotoxic T lymphocytes
B	Helper T lymphocytes
C	Mononuclear phagocytes
D	Natural killer cells
E	Preformed antibodies

2) A 60-year-old woman with type 2 diabetes and end-stage renal disease receives a kidney transplant. Three weeks later, the patient presents with azotemia and oliguria. If this patient has developed acute renal failure, which of the following pathologic findings would be expected on renal biopsy?	
A	Arterial intimal thickening and vascular stenosis
B	Glomerulosclerosis
C	Interstitial infiltrates of lymphocytes and macrophages
D	Neutrophilic vasculitis and fibrinoid necrosis
E	Tubular atrophy and interstitial fibrosis

3) A 47-year-old man with a history of a heart-lung transplant 3 years ago complains of fever, malaise, and abdominal pain. The patient has been taking cyclosporine for immunosuppression. Physical examination reveals an abdominal mass. A CT-guided biopsy of the mass shows atypical lymphocytes that are positive for latent membrane proteins of Epstein-Barr virus (EBV). What is the most likely diagnosis?	
A	Acute suppurative lymphadenitis
B	Burkitt lymphoma
C	Graft-versus-host disease
D	Infectious mononucleosis
E	Posttransplant lymphoproliferative disorder

4) A 19-year-old woman with chronic renal failure received a cadaver renal transplantation. One month later, she experienced increasing serum creatinine and urea nitrogen levels, and a renal biopsy was performed. She was treated with corticosteroids, and her renal function improved. Which of the following changes was most likely seen in the biopsy specimen before corticosteroid therapy was initiated?	
A	Interstitial infiltration by CD3+ lymphocytes and tubular epithelial damage
B	Extensive fibrosis of the interstitium and glomeruli with markedly thickened blood vessels
C	Fibrinoid necrosis of renal arterioles with thrombotic occlusion
D	Interstitial infiltration by eosinophils with tubular epithelial damage
E	Glomerular deposition of serum amyloid-associated protein

Thank you

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