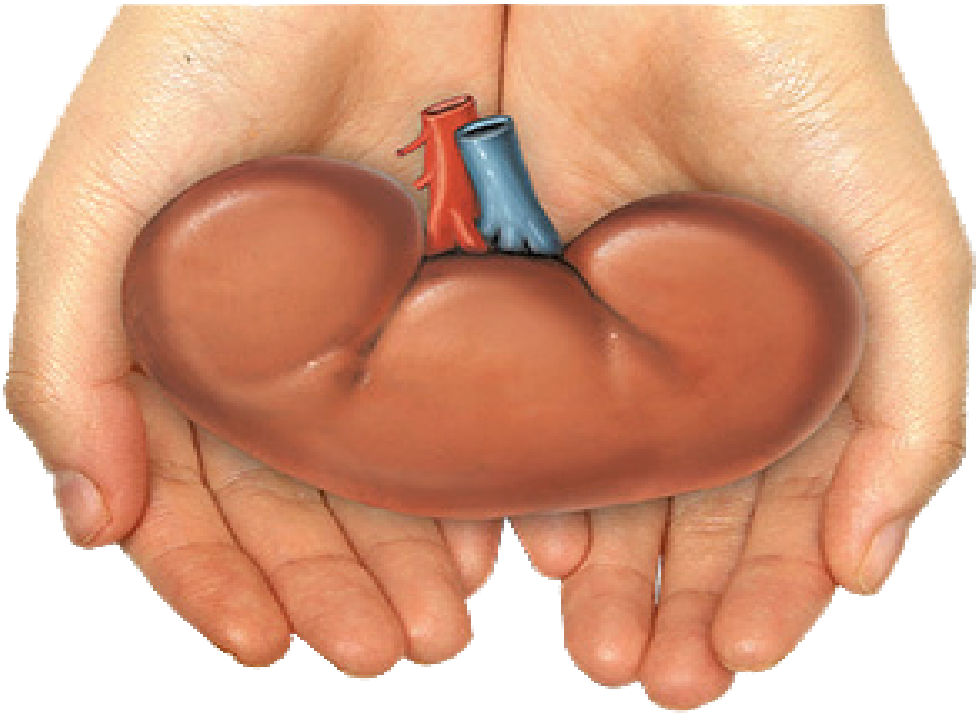
Renal Allograft



Objectives:

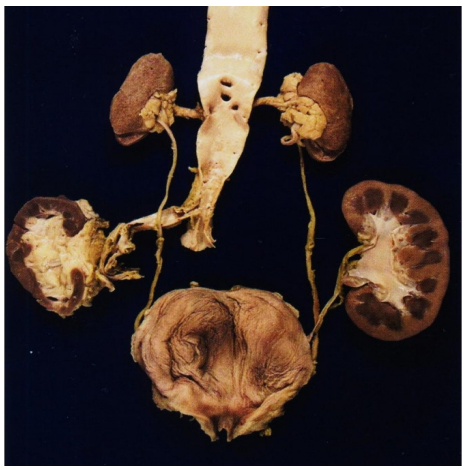
1. Recognize the concept of renal allograft.
   Describe the pathology of rejection and differentiate acute cell-mediated and antibody-mediated rejection.
2. Differentiate between acute and chronic rejection.
3. Brief account on principal opportunistic infections and drug toxicity encountered in renal transplant recipients.

Important note: During the previous blocks, we noticed some mistakes just before the exam and we didn't have the time to edit the files. To make sure that all students are aware of any changes, please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit.

Introduction.

The best treatment for kidney failure is transplantation (better than dialysis). Because the new kidney will be able to produce hormones & have a normal function.
The word **Allograft** refers to the transplantation of organs within the same species (human to human), while Xenograft refer to transplantation between different species (animals to human).

- A major barrier to transplantation is the process of rejection, in which the recipient's immune system recognizes the graft as being foreign and attacks it.



Notice that this patient has 4 kidneys, the upper two are the end-stage native kidneys in normal position. The atrophic first donor kidney (lower left), and the larger second donor kidney (lower right).
End-stage kidneys don't have to be removed, unless the patient is on dialysis because they will be prone to develop renal cell carcinoma or amyloidosis. So in this case they are removed.

Complications that may happen to transplanted kidney:

1. **Rejection.**
2. **No rejection:**
    - Infection (due to immunosuppressant drugs).
    - Drug toxicity.
    - Ischemia (anastomosis was not very will in surgery).
    - Recurrence of original disease (E.g MPGN, FSGS).
    - De novo GN.

Types of Renal Transplant Rejection: Robbins page 137 + 138

1. Normal.
2. Hyperacute Rejection → Circulating antibodies attack the allograft immediately (antibody mediated).
3. Accelerated acute rejection.
4. Borderline changes (very mild acute rejection).
5. Acute Rejection (T-cell or Antibody-mediated). -days to weeks-
6. Chronic Rejection.

Before we discuss the types of rejection, we should know the difference between T-Cell-mediated rejection & antibody-mediated rejection. Robbins page 137

T-Cell-Mediated Rejection.

Cytotoxic T lymphocytes kill cell in grafted tissue → parenchymal and endothelial cells death → Thrombosis and graft ischemia → cytokines secrete CD4 + T cells → accumulation of lymphocyte and activate macrophages → Graft Destruction (**Tubulointerstitial inflammation**).

Antibody-Mediated Rejection.

Antibody directed against Graft MHC → activation of complement and recruitment of leukocytes → Vascular injury and endothelial damage → Thrombosis and ischemia → Graft Destruction.

Immune Recognition of AlloGraft. Robbins page 135

Rejection of allograft is a response mainly to **MHC molecules.** **MHC molecules** are is a set of cell surface molecules encoded by a large gene family which controls a major part of the immune system. They are recognized by T-cells.

Next part is additional for better understanding.

There are *two main mechanism* by which the host immune system recognizes and responds to the MHC molecules of the graft:

1. Direct recognition:

Host T cells directly recognize the foreign MHC molecules that are expressed on graft cells.

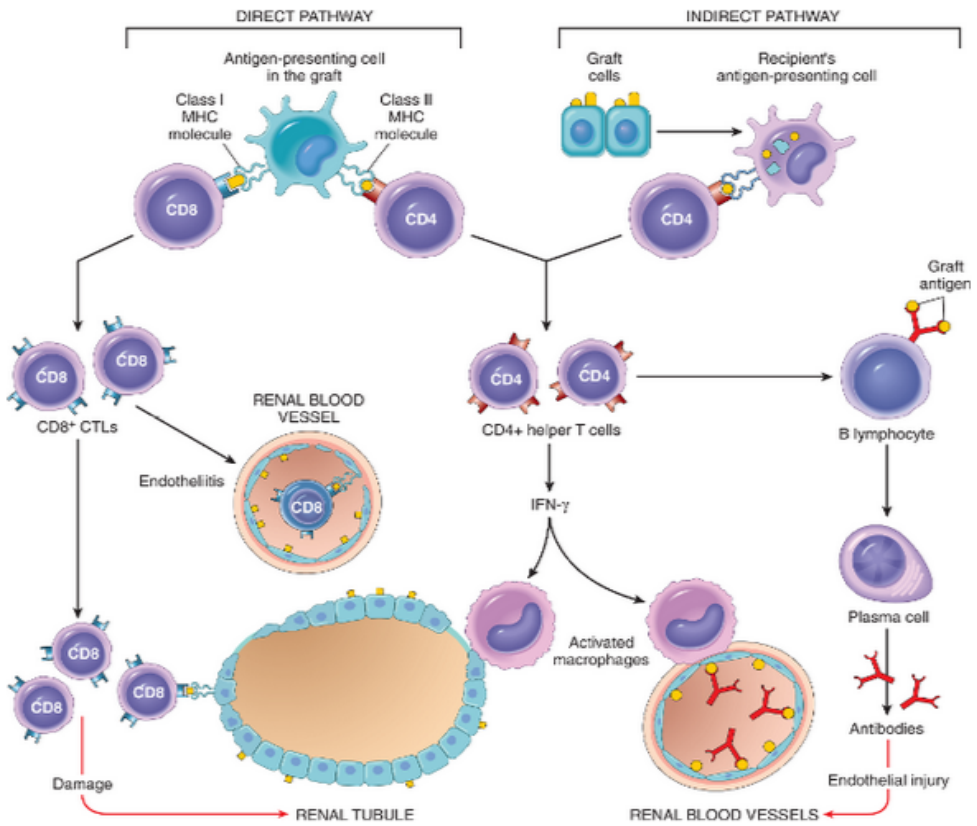
- It is suppose that allogeneic (foreign) MHC molecules (with any bound peptides) structurally mimic self MHC molecules with foreign peptides so the direct recognition of allogeneic MHC is essentially an **immunologic cross-reaction.**

The most important consequence of direct recognition is the activation of host CD8+ T cells that recognize class I MHC (HLA-A,B)molecules in the graft. These T cells differentiate into CTLs (cytotoxic T lymphocytes) which kill the cells in the graft.

Host CD4+ helper T proliferate and produce cytokines (e.g IFN-ϒ) which induced tissue damage by a local delayed-type hypersensitivity reaction and CD4+ helper T cells recognize donor class II MHC (HLA-D) molecules.

2. Indirect recognition:

Graft antigens are displayed by **host antigen presenting cells** and activate CD4+ helper T cells which produced cytokines that induce inflammation and damage the graft by a local delayed-type hypersensitivity and stimulate B lymphocytes to produce antibodies against the graft alloantigens.



Hyperacute Rejection.

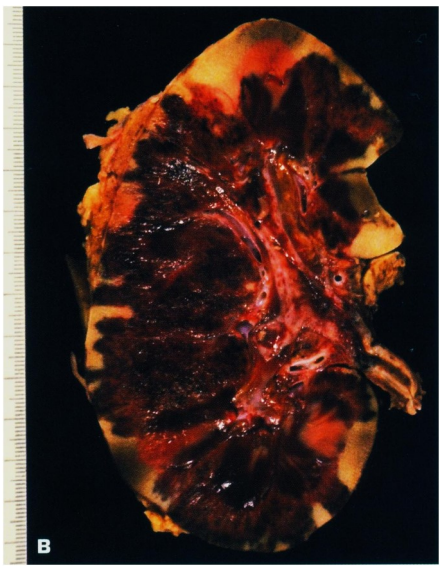
Rejection occurs within **minute to few hours** after transplantation in presensitized host and typically recognized by the surgeon just after the vascular anastomosis is completed.

It occurs if **preformed anti-donor antibodies are present in the circulation of the host before transplantation**, for example:

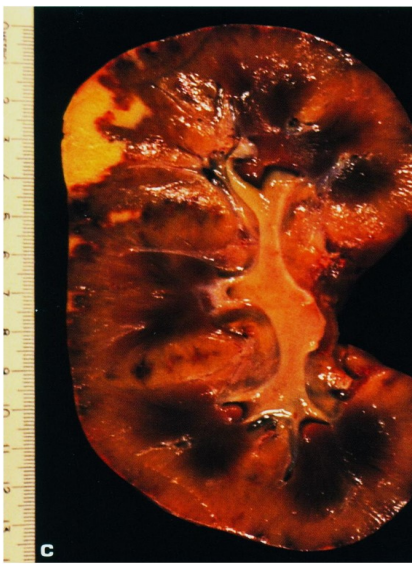
- In individual is exposed to foreign HLA (on platelets or leukocytes) from previous blood transfusions
- or such antibodies also may be present in a patient who has previously rejected an organ transplant.

Morphology after rejection: **Cyanotic[1], mottled[2] and flaccid[3]** and may excrete only a few drops of bloody fluid.

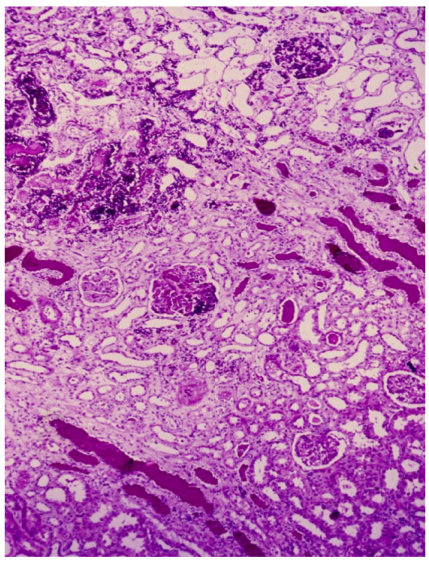
Under microscopy: Widespread acute arteritis and arteriolitis, vessel thrombosis and **fibrinoid necrosis**.



Subtotal renal infarction due to hyperacute (antibody-mediated) rejection.



Severe acute rejection of donor kidney, Focal infarcts are present.



Hyperacute Rejection under LM.

Accelerated acute rejection.

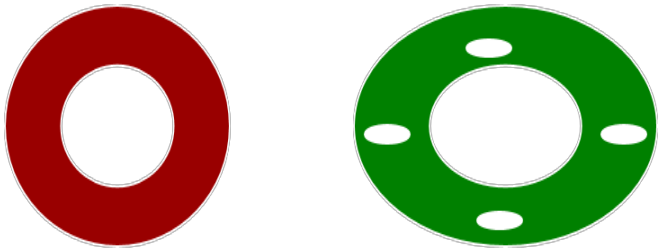
It occurs within hours or days and the patient may have **previous unsuccessful graft.**

- Caused by cellular or humoral immune mechanism.

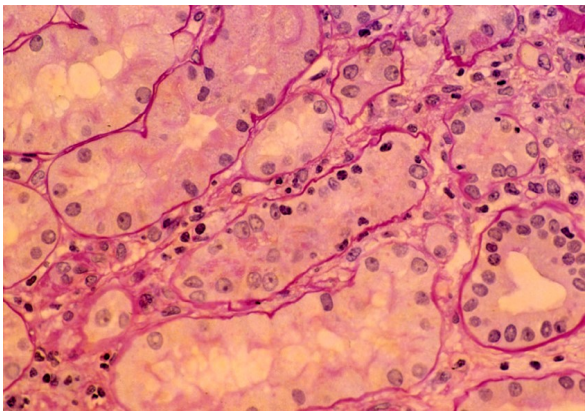
[1] زرقاء
[2] مبقعة
[3] رخوة

Borderline changes (very mild acute rejection).

It does not reach to acute rejection but it is not normal at the same time **(Suspicious)**. You may see interstitial inflammation with few tubulitis with **no intimal arteritis.**



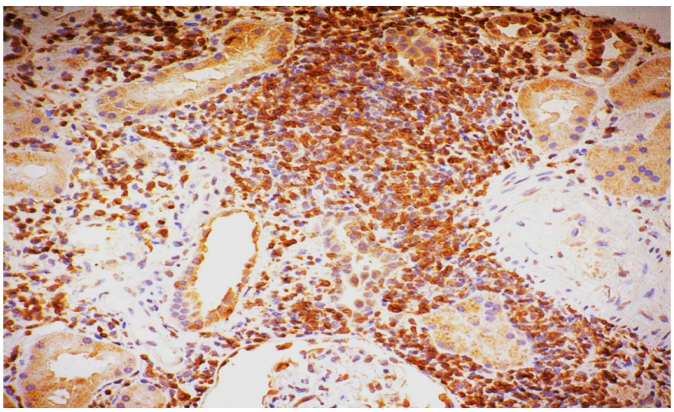
Borderline changes (Suspicious for Acute Rejection)



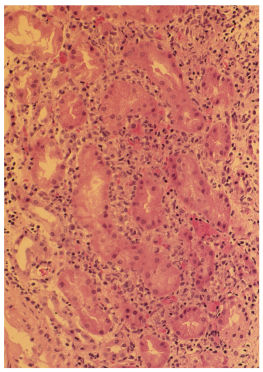
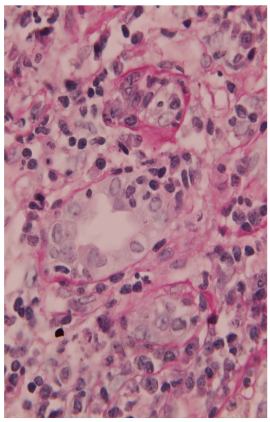
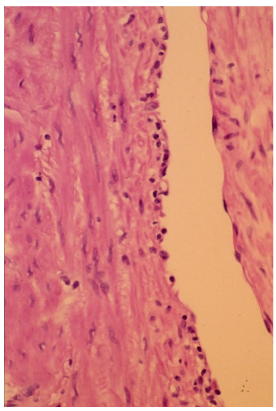
Acute rejection.

May occur within days to weeks and it can cause by both hormonal OR cellular immune response.

- **Acute cellular rejection:** T cells will destroy parenchyma by cytotoxic and inflammatory cells.
- **Acute hormonal rejection:** Antibody damage graft vasculature.



The interstitial infiltrate consists of T cells mainly.

The Banff classification in acute rejection				
Grade I	**A**	Mononuclear interstitial inflammation (>25%). Moderate tubulitis. (5 to 10).		
	B	Mononuclear interstitial inflammation (>25%). Severe tubulitis (>10).		
Grade II	**A**	Mild to Moderate intimal arteritis.		
	B	Severe intimal arteritis.		
Grade III		Transmural arteritis and/or fibrinoid necrosis.		

Chronic Rejection.

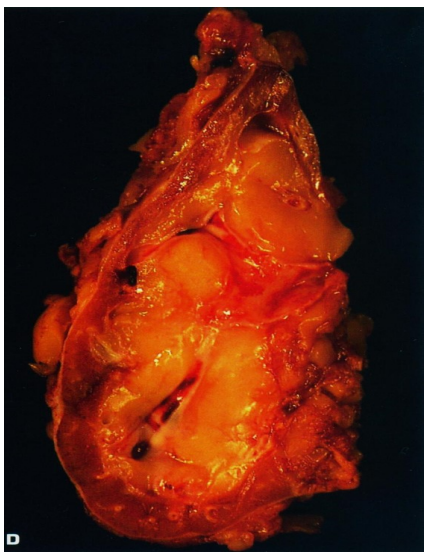
Patients present with chronic rejection late after transplantation (months to years). In those patients their will be elevation in **serum creatinine** (which is an index in impaired renal function). Chronic rejection is characterized by:

- **Vascular Sclerosis:** Changes in arteries and arterioles which exhibit intimal smooth muscle cell proliferation and extracellular matrix synthesis. The vascular changes may be caused by cytokines that is secreted by **T cells.**
- Renal **ischemia caused by: interstitial fibrosis**, loss of glomerular hyalinization and tubular atrophy.
- Loss in renal parenchyma.

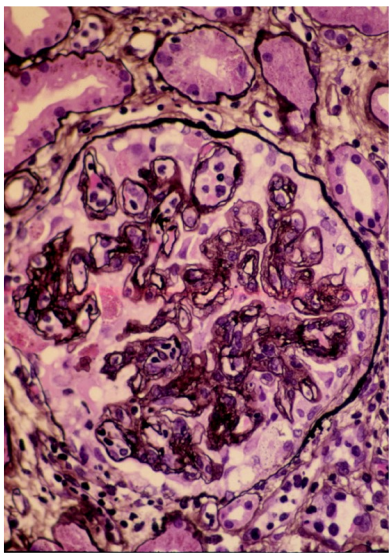
The Banff classification in chronic rejection:

1. Grade I (Mild).
2. Grade II (Moderate).
3. Grade III (Severe).

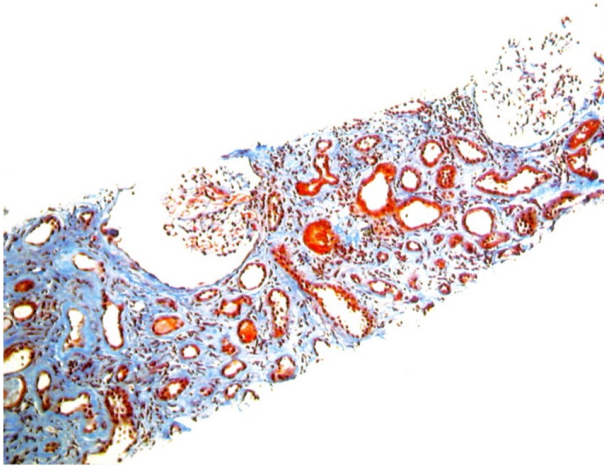
- **Normal, Suspicious** → No Treatment (We measure creatinine level if it's high we treats the patient, if it's normal we follow him up).
- **Grade I** → Treat if clinical signs +.
- **Grade II** → Treat.
- **Grade III** → Treat or Abandon.
- **Cyclosporine toxicity** → Reduce Cyclosporine.
- **Acute Tubular Necrosis** → Await recovery or treat.
- **Chronic rejection** → Temporize.



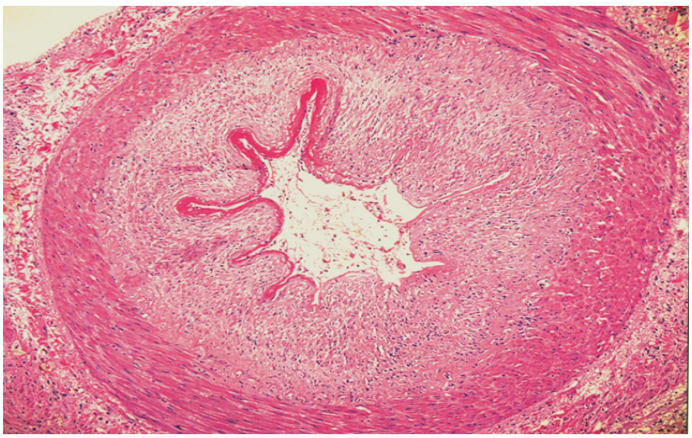
Severe chronic rejection, (graft arteriopathy). Note the severe parenchymal atrophy and the thick-walled arteries.



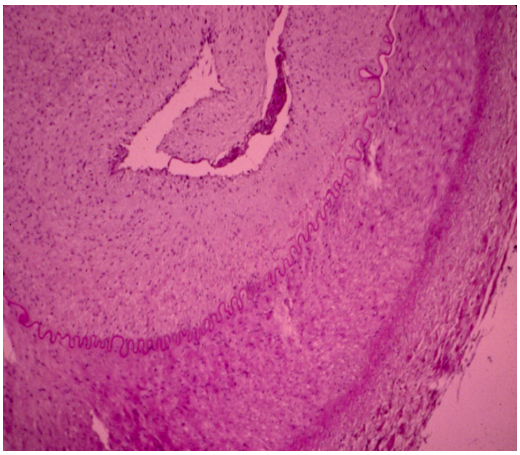
Frequent **double contours** along the glomerular capillary loops



An example of Grade II-III is characterized by a diffuse increase in interstitial tissue and marked tubular atrophy as seen on this trichrome stain.



The classical lesion of **chronic transplant vasculopathy** is a circumferential proliferation of myointimal cells with an intact internal **elastic lamina**.



Chronic vasculopathy related to acute rejection.

SUMMARY

Recognition and Rejection of Organ Transplants (Allografts)

- The graft rejection response is initiated mainly by host T cells that recognize the foreign HLA antigens of the graft, either directly (on APCs in the graft) or indirectly (after uptake and presentation by host APCs).
- Types and mechanisms of rejection comprise the following:
  - *Hyperacute rejection*: Pre-formed antidonor antibodies bind to graft endothelium immediately after transplantation, leading to thrombosis, ischemic damage, and rapid graft failure.
  - *Acute cellular rejection*: T cells destroy graft parenchyma (and vessels) by cytotoxicity and inflammatory reactions.
  - *Acute humoral rejection*: Antibodies damage graft vasculature.
  - *Chronic rejection*: Dominated by arteriosclerosis, this type is probably caused by T cell reaction and secretion of cytokines that induce proliferation of vascular smooth muscle cells, associated with parenchymal fibrosis.

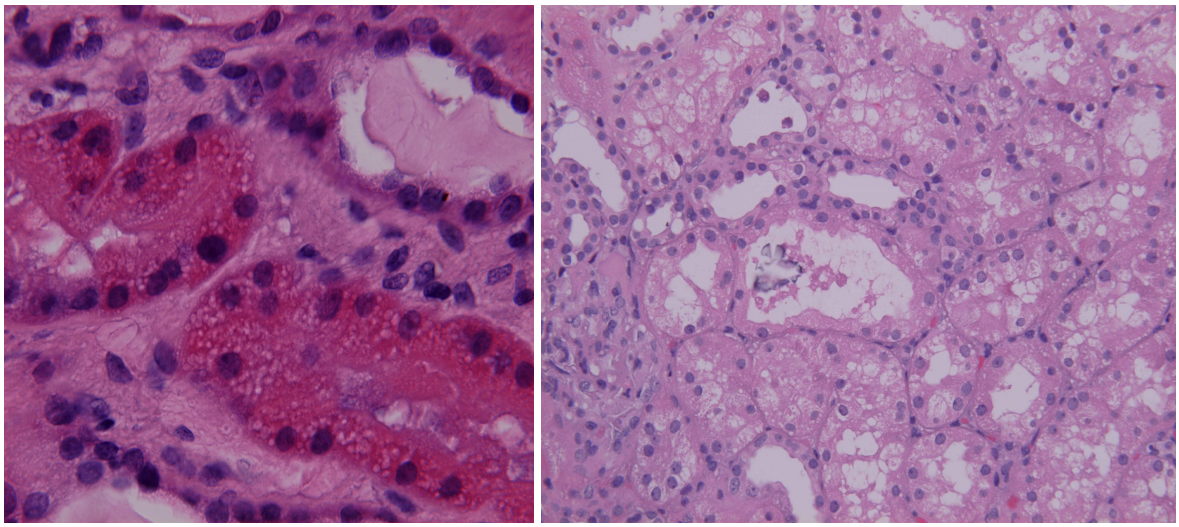
Drug Toxicity.

The immunosuppressant drugs used with transplantation is toxic to the kidneys (dose must be adjusted if its toxicity occurs).

- Its difficult to differentiate between drug toxicity and chronic rejection.

Drugs Toxicity	Biopsy	Comment
Acute Drugs Toxicity	**Isometric vacuoles**[4] in the tubular epithelial cells.	That means you should adjacent the dose (it is too high).
Chronic Drugs Toxicity	1. Nodular hyaline in the wall of blood vessel. 2. Interstitial fibrosis	-

• **Ischemia may cause isometric vacuoles** also so we should check the drug level in the blood to know the etiology whether it's ischemia or drug toxicity.



Nodular hyaline in the wall of blood vessel and Interstitial fibrosis (chronic Drug Toxic).
Right picture: Calcification of necrotic tissue in the tubules.

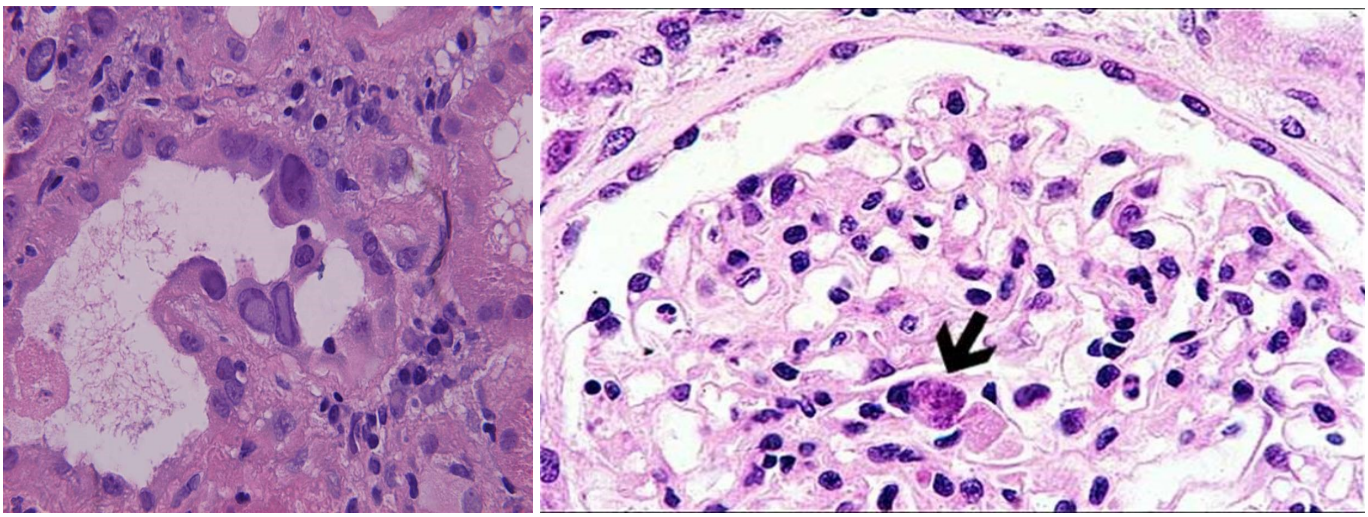
4

Infections.

That may happen due to high dose of immunosuppressant drugs.

Viral infections:

Virus	Biopsy	Comment
Cytomegalovirus (cmv)	1- Increases the cells size in all part of the kidney. 2- Inflammatory cells infiltrate	With high dose, make sure there is no increase in the cells size.
Polyomavirus (sv40)	Glassy nuclei	Only infect the kidney mainly DCT. **Special stains is used for investigation**



Arrow: Cell infected by cytomegalovirus.

Conclusion:

The Banff classification has proposed a schema[5] for interpretation and gradation of the histological findings in renal allograft biopsies that can be used as an indication for therapeutic consequences and expected graft survival.

[5] theory or plan

MCQ's.

The major molecules responsible for transplant rejection is?

A.T cell
B.Antibodies
C.MHC molecule
D.B cell

Anc:C

The Direct pathway of graft rejection happen by:

A.Antigen presenting cell in the recipient .
B.Antigen presenting cell in the graft .
C.Using antibodies.
D.None of them.

Anc:B

Which one of the following is infection associated with glassy nuclei?

A.Polyomavirus
B.cytomegalovirus(cmv)
C.Both of them.
D.Neither

Anc:B

Antibodies damage graft vasculature in

A.Grade III acute rejection .
B.Acute cellular rejection
C.Acute humoral rejection
D.Chronic rejection

Anc:C

Hyperacute rejection lead to?

A.Ischemic necrosis
B.Interstitial fibrosis
C.Endotheliitis
D.Atrophy

Anc:A

Occurs in a patient who had a previous unsuccessful graft?

A.Accelerated acute rejection
B.Chronic rejection
C.Acute rejection
D.Borderline

Anc:A

SAQs.

1- What are cells that can recognize the MHC donor by indirect recognition?
CD4 + T-helper cells.

2- What can you see in Biopsy of chronic kidney drug toxic?
Nodular hyaline and fibrosis.

Contact us on: Pathology434@gmail.com
@Pathology434, **Ask us!**

Good Luck!

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