LECTURE 7*:
Pathology of Renal allograft

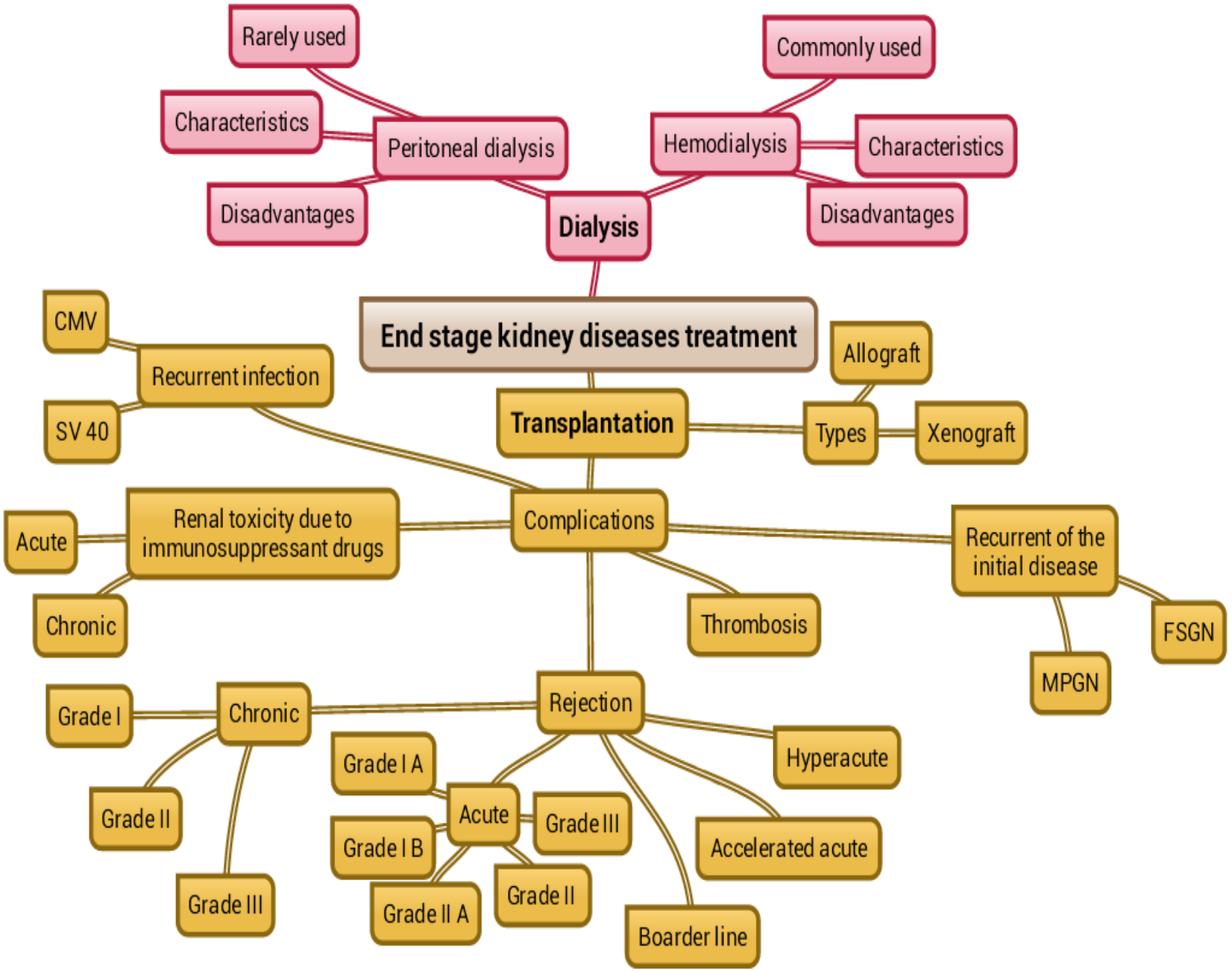
*It’s the last lecture in the renal block and first year, we wish we helped you to make pathology easier for you, good luck in the exam and happy vacation ;D

OBJECTIVE

At the end of the lecture, the students should be able to

I. **Recognize the concept of renal allograft**
II. **Describe the pathology of rejection and differentiate acute cell-mediated and antibody-mediated rejection**
III. **Differentiate between acute and chronic rejection**
IV. **Brief account on principle opportunistic infections and drug toxicity encountered in renal transplant recipients**

MIND MAP


Rarely used
Characteristics
Peritoneal dialysis
Disadvantages
Commonly used
Hemodialysis
Characteristics
Disadvantages
Dialysis
End stage kidney diseases treatment
CMV
Recurrent infection
SV 40
Allograft
Transplantation
Types
Xenograft
Acute
Renal toxicity due to immunosuppressant drugs
Chronic
Complications
Recurrent of the initial disease
FSGN
MPGN
Thrombosis
Grade I
Chronic
Grade II
Grade III
Rejection
Grade I A
Grade I B
Acute
Grade II A
Grade III
Grade II
Hyperacute
Accelerated acute
Boarder line

Dialysis

- **Is a mechanical process that performs the work that healthy kidneys would do. It clears wastes and extra fluid from the body and restores the proper balance of chemicals (electrolytes) in the blood.**
- **Dialysis comes in two types:**

Hemodialysis

Is a medical procedure that uses a special machine to filter waste products from the blood and to restore normal constituents to it.

Characteristics of hemodialysis:

1- Using a special machine in the hospital
2- Inserted in the blood stream
3- Ones every few weeks to few months
4- Each Hemodialysis take a few hours

Disadvantages of hemodialysis:

1- Transmission of diseases due to poor sterilization of the dialysis machine
2- Infections (HIV, HBV, Syphilis)
3- Thrombosis
4- Destruction of the vessels due to continuous use
5- Not available in every hospital

Peritoneal dialysis

(Or continuous ambulatory peritoneal dialysis (CAPD)

Peritoneal dialysis is the removal of soluble substances and water from the body by transfer across the peritoneum, utilizing a solution which is intermittently introduced into and removed from the peritoneal cavity.

Characteristic of peritoneal dialysis:

1- Catheter inserted into the peritoneal cavity
2- The patient is ambulatory
3- Can be used any ware
4- Daily use

Disadvantage of peritoneal dialysis:

1- More prone to cause infections
2- 3 to 5 daily use dialysis

This slide was mentioned by Dr.alrikabi
And it is not from the objectives of the lecture

Introduction of transplantation

- **Organ transplantation** is increasly used to treat irreversible diseases of the kidney, liver, heart, lung and bone marrow.

- Unfortunately, the action of the immune system can lead to the transplanted tissue being destroyed, a process termed **transplant rejection**. For the best chance of survival, antigens in the graft and recipient must be matched.

- 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).

Introduction of transplantation

- The problems of renal transplant are:

1- Renal allograft transplant rejections, which are divided into:

I. **Hyperacute rejection**
II. **Accelerated acute rejection**
III. **Boarder line rejection**
IV. **Acute rejection**
V. **Chronic rejection**

2- Recurrent of the initial disease (usually are FSGN*, MPGN*)

3- opportunistic infections or Renal toxicity (due to immunosuppressant drugs)

4- thrombosis of surgical vascular anastomoses (due to inadequate surgical skills)

*Focal segmental glomerulonephritis

*Membranoproliferative glomerulonephritis

Mechanism of graft rejection

- There are two ways of graft rejection:

1. Direct :

Class I and class II major histocompatibility antigens (MHC) on antigen presenting cells of the donor are recognized by the recipient, **CD8+ suppressor T cells** and **CD4+ T helper cells** respectively. CD4+ T cells proliferate **produce cytokines which induce tissue damage to renal blood vessels and tubules by a hypersensitivity reaction**.

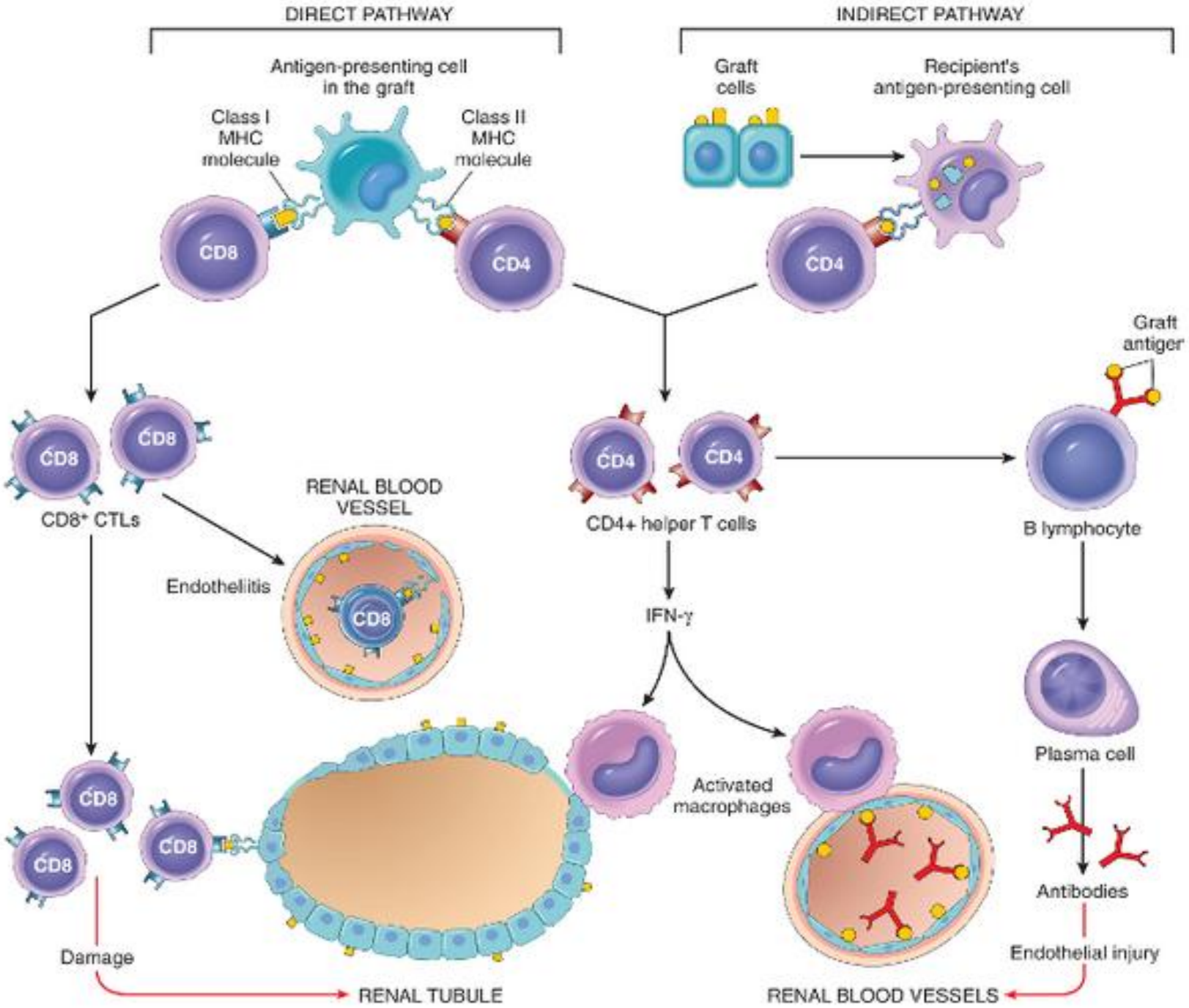
2. Indirect :

graft antigen are taken by the antigen presenting cells in the recipient. These APCs activate CD4+ cells which damage the graft by a local delayed hypersensitivity reaction and stimulate B lymphocytes to produce **antibodies**.

- To prevent rejection and transplanting complications, we should:

1. Check blood groups.
2. HLA typing* (looking for identical twins because they have similar HLA)

*Human leukocyte antigen (HLA) is a group of proteins encoded by certain genes that found in chromosome 6, and they encode for specific proteins for the person. And we have three types of HLA: HLA-A, HLA-B, HLA-DC,HLA-DP, HLA-DQ and HLA-DR .


DIRECT PATHWAY
INDIRECT PATHWAY
Antigen-presenting cell in the graft
Class I MHC molecule
Class II MHC molecule
Graft cells
Recipient's antigen-presenting cell
CD8
CD4
CD8+ CTLs
RENAL BLOOD VESSEL
Endothelitis
CD4+ helper T cells
IFN-γ
B lymphocyte
Graft antiger
Plasma cell
Activated macrophages
Antibodies
Damage
RENAL TUBULE
Endothelial injury
RENAL BLOOD VESSELS

Types of graft rejection

1- Hyperacute rejection

- Occurs within minutes or few hours after transplantation, hyper acute rejection is rejecting kidney by circulating antibodies*(cause endothelial damage) . The kidney rapidly becomes cyanotic, mottled (منقط) and flaccid (رخو) and may excrete only few drops of bloody fluid and it doesn't produce urine. It leads to thrombosis, ischemic damage and graft failure. The histologic picture is widespread acute arteritis and areteriolitis, vessel thrombosis and ischemic necrosis (coagulative necrosis).

*This happen due to recipient high immunity because:

1. Bad cross matching of HLA.
2. Previous blood transfusion.
3. Previous graft.

- Now because advanced investigation this type is rarely happened.

2- Accelerated acute rejection

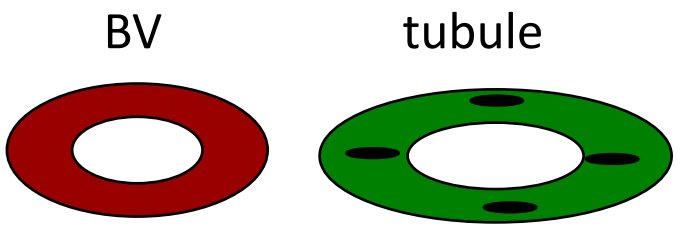
- It occurs within hours or days and the patient may have previous unsuccessful graft.
- Caused by cellular or humoral immune mechanism.

This was mentioned by Dr. alrikabi

3- Boarder line rejection (Suspicious= مشبوه)

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

This was mentioned by Dr. hala



*it is not involve 25% which makes it acute.

4- Acute rejection

Occurs within days to weeks of transplantation, caused by both cellular and humoral immune mechanisms, and both may be present in one patient. On histologic examination **cellular rejection** is marked by: Interstitial mononuclear cell infiltrate with edema and parenchymal injury, whereas **humoral rejection** is associated with vasculitis.

1. **Acute cellular rejection**: Commonly seen within months after transplantation. For the histologic features, it shows CD4 and CD8 with T cell infiltration and edema. CD8 and T cells may injure the endothelium **causing endotheliitis and focal tubular necrosis** .

2. **Acute humoral rejection (rejection vasculitis)**: Caused by antidonor antibodies. Histological, we may see necrotizing vasculitis with endothelial cell necrosis, neutrophilic infiltration, complement and fibrin. The narrowing of the arterioles may cause infarction or renal cortical atrophy.

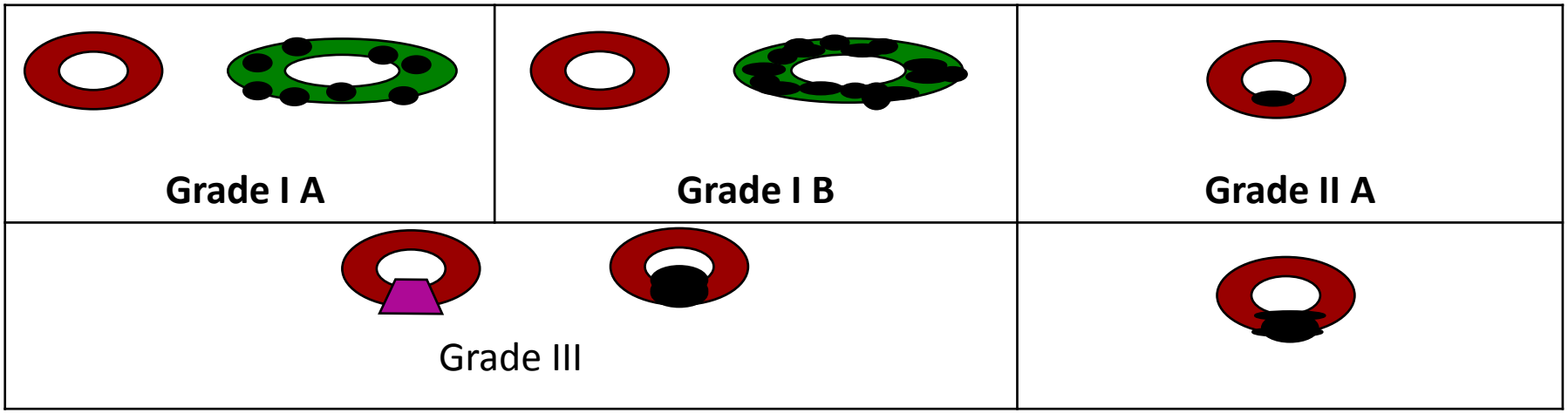
N.B: Acute rejection may associated with tubulitis, which mean ''four or more T lymphocyte are infiltrate in one tubule'', and it's reversible if treated.

4- acute rejection

This was mentioned by Dr. hala

The Banff classification

- Grade I A :→Mononuclear interstitial inflammation(>25%)→+ Moderate tubulitis.(5 to 10)
- Grade I B :→Mononuclear interstitial inflammation(>25%)→+Severe tubulitis(>10)
- Grade II A: Mild to Moderate intimal arteritis
- Grade II B: Severe intimal arteritis
- Grade III →Transmural arteritis and/or fibrinoid necrosis.



5- Chronic rejection

- Occurs within months to years after transplantation
- progressive rise in serum creatinine.
- Chronic rejection is dominated by vascular changes, interstitial fibrosis , loss of renal parenchyma and tubular atrophy .
- The vascular changes occur in the arteries and arterioles, which exhibit **intimal smooth muscle cell proliferation** and **paranchymal fibrosis lead to ischemia**. This type is probably caused by T cells reaction and secretion of cytokines.

The Banff classification

Chronic Allograft Nephropathy:

- Grade I (Mild)
- Grade II (Moderate)
- Grade III (Severe)

This was mentioned by Dr. hala

Drugs toxicity

- The immunosuppressant drugs that is used with transplantation could be toxic on transplanted kidney.
- It is difficult to differentiate between drugs toxicity and chronic rejection.

Types	Acute drugs toxicity	Chronic drugs toxicity
Biopsy	• Isometric vacuoles in the tubular epithelial cells • Ischemia may occurs	▪ Nodular hyaline in the wall of blood vessel . ▪ Interstitial fibrosis
Comment	That means u should adjacent the dose (it is too high)	

This slide was mentioned by Dr. hala

Infection

- That may happen due to high dose of immunosuppressant drugs.

Organism	Cytomegalovirus (CMV)	POLYOMAVIRUSE (SV 40)
Biopsy	• Inflammation infiltrate * • Increases the cells size in all part of the kidney. (from this point it gets this name)	Glassy nuclei
Comment	*Be careful at this point don't think of rejection and higher the dose+ make sure there is no increase in the cells size.	❑ This is only infected the kidney mainly DCT. ❑ Used special stains to investigate it

This slide was mentioned by Dr. hala

TYPES OF REJECTION	Hyperacute rejection	Accelerated acute rejection	Acute Rejection		Chronic rejection
TIME	Minutes or few hours	Hours or days	Days to weeks sometimes months to years later		months to years
Mechanism	Rejecting kidney by circulating antibodies	Previous unsuccessful graft	**Acute Cellular rejection (direct)**	**Acute humeral rejection(indirect**	Progressive rise in serum creatinine
				Caused by antidonor antibodies	
Change	becomes cyanotic, mottled flaccid few drops of bloody fluid and it doesn't produce urine	Caused by: cellular or humoral immune mechanism	CD8 and T cells may injure the endothelium **causing endotheliitis and focal tubular necrosis**	The narrowing of the arterioles may cause infarction or renal cortical atrophy.	
Banff Classification	-	-	Grade I A: Mononuclear interstitial inflammation + Moderate tubulitis Grade I B :Mononuclear interstitial inflammation +Severe tubulitis Grade II A: Mild to Moderate intimal arteritis Grade II B: Severe intimal arteritis Grade III →Transmural arteritis and/or fibrinoid necrosis		Grade I (Mild) Grade II (Moderate) Grade III (Severe)
Histologic Picture	acute arteritis and areteriolitis, vessel thrombosis and ischemic necrosis (coagulative necrosis	-	it shows CD4 and CD8 with T cell infiltration and edema	may see necrotizing vasculitis with endothelial cell necrosis, neutrophilic infiltration, complement and fibrin	-

MCQs

1/ Which one is NOT disadvantage of Hemodialysis?

A. Transmission of diseases due to poor sterilization
B. Thrombosis
C. Frequently used
D. None of these

2/ The transfer of tissue between genetically different individual with same species?

A. Xenograft
B. Autograft
C. Allograft
D. None of these

3/ Hyper acute rejection lead to?

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

4/ Occurs in a patient who had a previous unsuccessful graft?

A. Accelerated acute rejection
B. Chronic rejection
C. Acute rejection
D. Boarder line

1- C
2- C
3- A
4- A

MCQs

5/ More than 4 T lymphocytes in the tubular epithelium lead to Tubilitis (endotheliitis), then lead to?

A. Acute humoral rejection
B. Chronic rejection
C. Hyper acute rejection
D. Acute cellular rejection

6/ What is the characteristic of chronic rejection?

A. Endothilitis
B. Thrombosis
C. Graft failure
D. Interstitial and intimal Fibrosis

7/ Recurrent of initial disease in the transplanted kidney such as?

A. Membranoproliferative GN
B. Alport syndrome
C. Acute proliferative GN
D. Rapidly progressive glomerulonephritis

8/ The major molecules responsible for transplant rejection is?

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

5- D
6- D
7- A
8- C

MCQs

9/ During transplant surgery, the patient lost a lot of blood, so the surgeon had to transfuse blood and lead to?

A. Hyper acute rejection
B. Acute rejection
C. Cellular acute rejection
D. Chronic rejection

10/ 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.

11/ Acute cellular rejection present with destroy graft parenchyma and vessels by?

A. Cytotoxicity and inflammatory reactions mediated by T cells
B. Antibodies producing from plasma cell
C. Cytokinase
D. None of them.

12/ Antibodies damage graft vasculature in

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

13/which one of the following is infection associated with glassy nuclei?

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

9-A
10-B
11-A
12-C
13-A

QUESTIONS

1- Hyperacute rejection is preformed antidonor antibodies bind to graft endothelium immediately after transplantation , what does this rejection lead to?

1- thrombosis

2- ischemic damage

3- rapid graft failure

2- How does the graft reject initially?

Mainly by host T cells that recognize the foreign HLA antigens of the graft either directly or indirectly .

3- What will happen to the serum creatinine when kidney transplantation fails?

It will be raised

4- What is the histopathological finding of acute drug toxicity?

Small vacuoles in the cytoplasm of the cell.

5- What are the histopathological findings of chronic drug toxicity?

we look for 2 things:

1- hyaline nodules in the wall of the blood vessels

2-interstitial fibrosis

6- What is dominant in the chronic rejection?

arteriosclerosis and proliferation of vascular smooth muscle cells and it is associated with parenchymal fibrosis .

Team Member's

Abdulrahman Al-Thaqib
Othman Abid
Omar Aldhasee

Maha Alzahrani
Amjad Albatili
Ghadah Alhammad

Contact us:
Pathology433@gmail.com
@pathology433