Renal allograft

تعود هذه الصورة لبداية زراعة الأعضاء وهي مذكورة في أحد روايات الروم الكاثوليك في القرن الثالث الميلادي من قبل الطبيبان دميان وقزمان والتي تعود أصولهم إلى أصول عربية ، حيث تم استبدال قدم الشماس الروماني بقدم أثيوبي متوفى

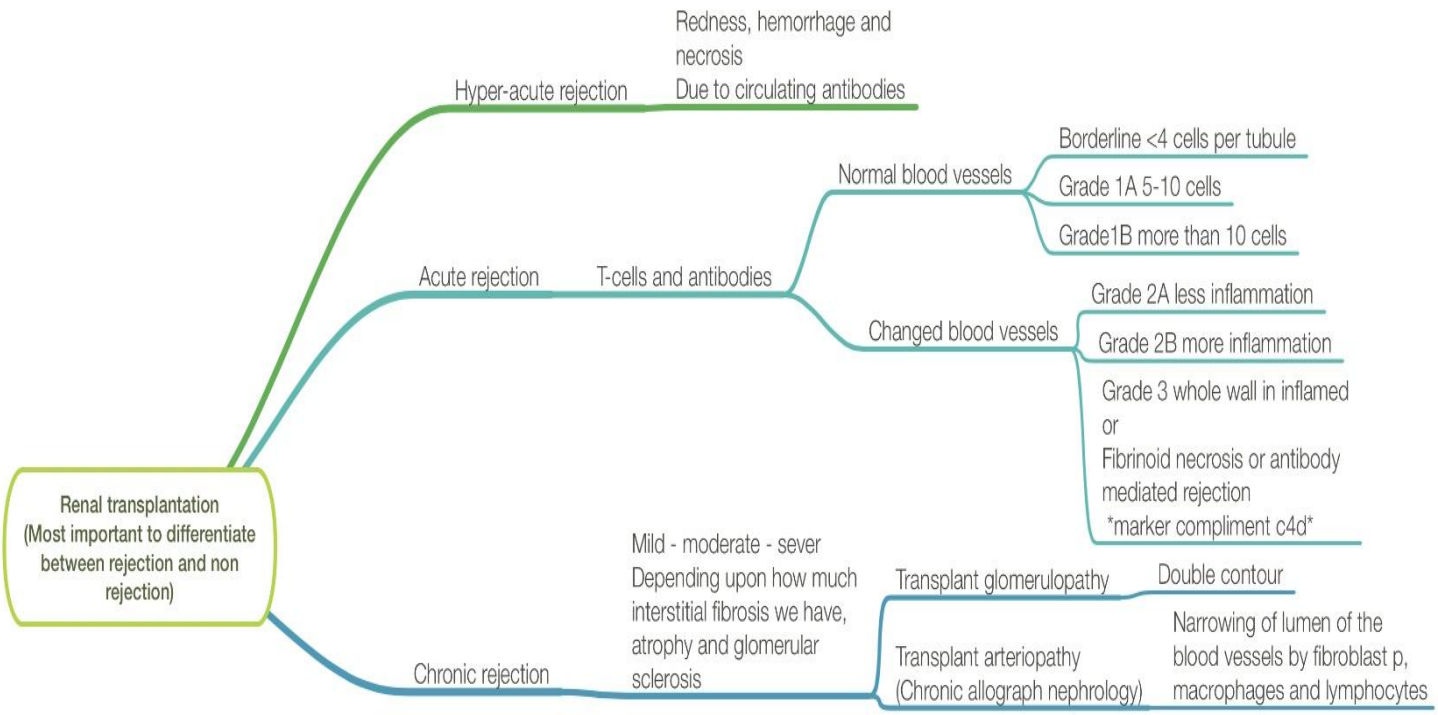
Objectives

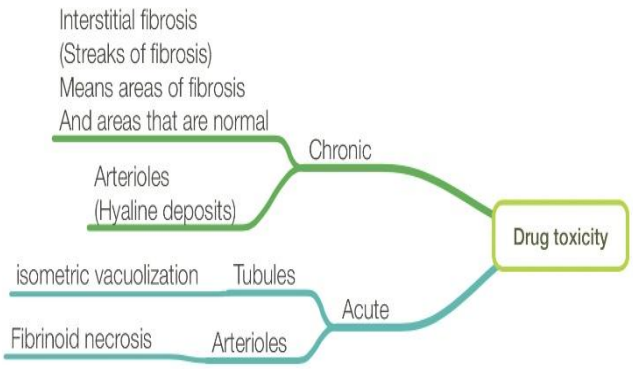
- Recognize the concept of renal allograft.
- Describe the pathology of rejection
- Differentiate between acute and chronic rejection.
- Recognize the principal infections inherent to renal transplantation.
- Recognize acute and chronic drug toxicity.

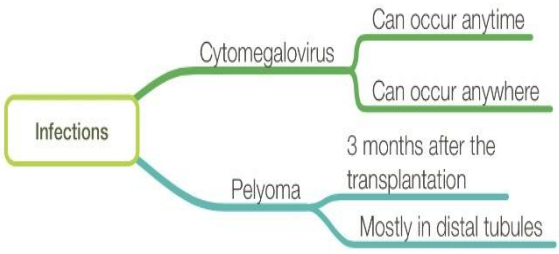
*Important *Doctor notes

Overview

Very important



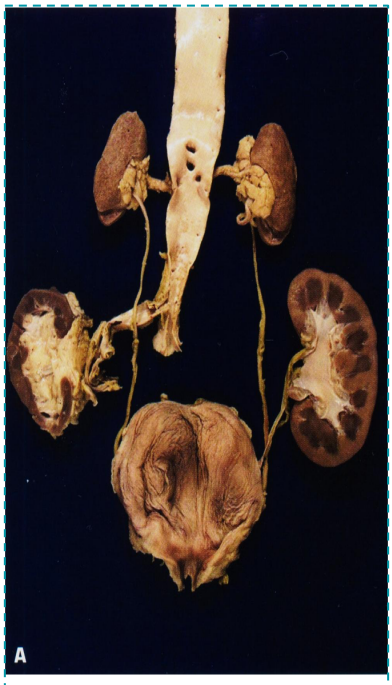




*C4d useful markers of antibody-mediated rejection in solid organ transplants.

Introduction

- The major barrier to transplantation of organs from one individual to another of the same species (allograft) is **immunological rejection** of the transplanted tissue.
- The word **allograft** refers to transplantation of organs within the same species while **xenografts** refer to transplantation between different species.
- **Rejection** is a complex phenomenon involving both cell and antibody mediated hypersensitivity reactions directed against the histocompatibility molecules of the foreign graft.
- The key to successful transplantation has been the development of therapies (drugs) that prevent or minimize rejection.*
- Rejection of allograft is a response mainly to MHC molecules which are so polymorphic that most individuals in an outbred population differ in at least some of MHC molecule they express, except identical twins**.

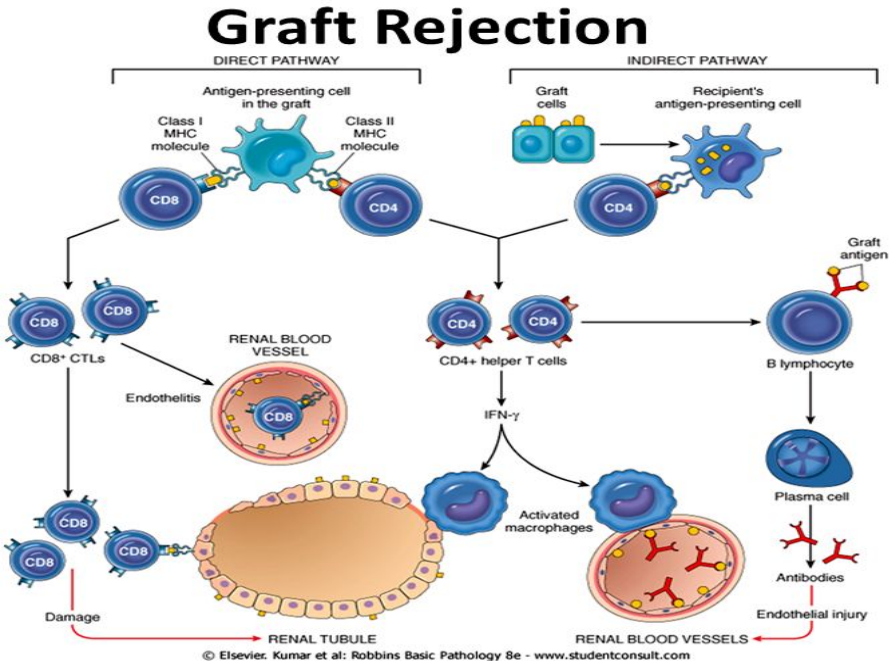


Renal transplantation
Note the two end-stage native kidneys in normal position, the atrophic first donor kidney (lower left), and the larger second donor kidney (lower right)

*Extra:Since these drugs affect rejection they shouldn't always be taken because they might affect the immune system making it unable to defend properly.

**لذلك قبل اجراء العملية يتم التأكد من تطابق او على الأقل وجود تشابه للحد من الضرر وسهيل قبول الجسم العضو بالنسبة للتوائم المتماثلة نسبة الفرق بينهم قليلة جدا وبالتالي نسبة الضرر وعدم قبول الجسم للعضو تقل أيضا

- **There are two main mechanism by which the host immune system recognizes and response to the MHC molecules on the graft:**



While it is the **host** that usually rejects the graft, note that the **graft** can "reject" the host (as in graft vs. host disease) – this happens when T-cells from the graft react against the host tissues

1-Direct recognition:

Host cells[1] directly recognize the allogenic (foreign)(pathogen) MHC molecules that are expressed on graft cells. Direct recognition of the allogeneic MHC is essential an immunologic cross-reaction.(Most common graft cell recognize is dendritic cell, due to high level of MHC molecules)

Mechanism of direct recognition: the most important consequence of direct recognition is:

a. activation of host CD8+T cells[2] by recognizing class1 MHC (HLA-A, -B) molecules in the graft
b. **Then** CD8 T cells differentiate into CTLs (cytotoxic T lymphocytes) Kill the cells.
c. CD4+ helper T cells may be triggered into proliferation and cytokine production by: recognition of donor class11 MHC (HLA-D) molecules and drive an inflammatory response.
d. This Activated in **acute** mainly

2-indirect recognition:

In this pathway CD4+ T cells recognize donor class2 MHC molecules after these molecules are picked up and processed, they are present by the hosts own APCs, the CD4+ will recognize it and secret cytokines that induce inflammation and damage the graft (anti-body here play role)

- This Activated in **chronic** mainly

- CD4 recognizes MHC2 molecules.
- CD8 recognizes MHC1 molecules.

Effector mechanism of graft rejection:

Both **T cells** and **antibodies** reactive with the graft are involved in the rejection of most solid-organ allograft

T-Cell-Mediated Rejection:

A- Cytotoxic T cells directly kill cell in **grafted tissue causing parenchymal and endothelial cells damage.**

B. **Results** in thrombosis and graft ischemia.

C. CD4 T-cells secrete cytokines that cause infiltration of inflammatory cells and activations of macrophages that cause damage.

Antibody-Mediated Rejection

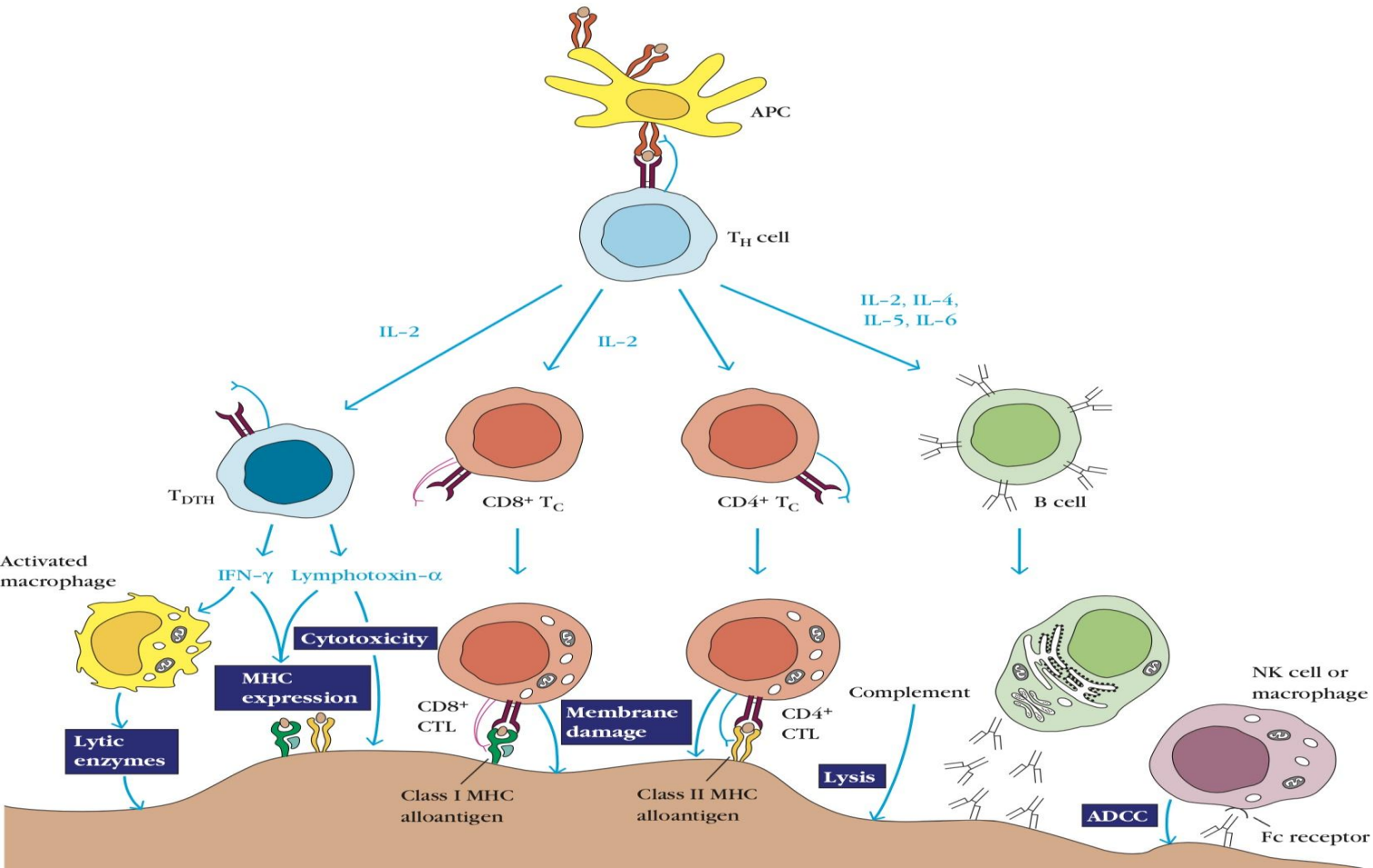
A. Antibody directed against **Graft MHC**

B. activation of **complement**

C. Vascular injury and recruitment of leukocytes

D. Thrombosis and ischemia

E. endothelial damage Destruction.



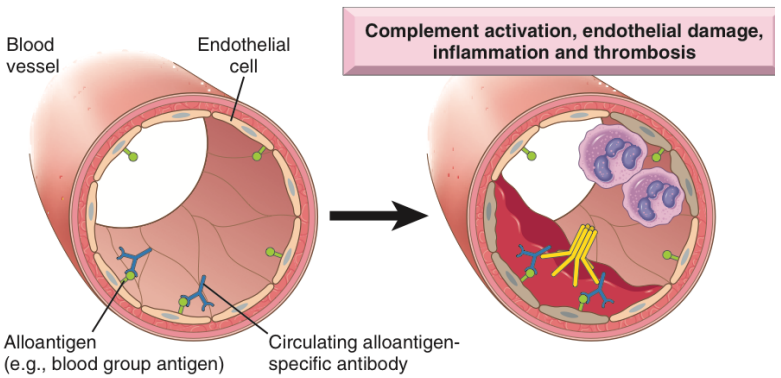
The Banff Classification: Diagnostic Categories
Rejection reaction has been classified as Hyperacute, acute, chronic

- Normal
- Hyperacute Rejection (Antibody-mediated)
- Borderline changes ("very mild acute rejection")
- Acute Rejection (Tcell, Antibody-mediated)
- Chronic Rejection
- Others

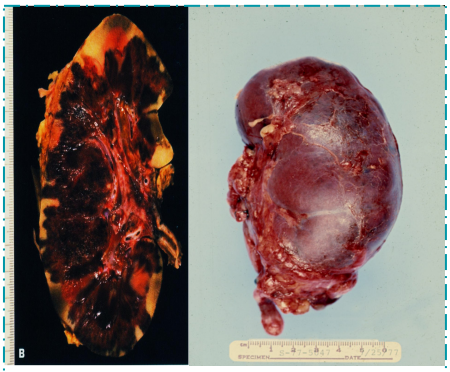
Hyperacute Rejection (Antibody mediated endothelial damage) May be natural IgM

Occurs within minutes to a few hours after transplantation in a presensitized host and is typically recognized by the surgeon just after the vascular anastomosis is completed. Grossly, the kidney becomes **cyanotic , mottled, flaccid, may excrete a few drops of bloody fluid** Microscopically, there is widespread acute arteritis and arteriolitis, vessel thrombosis and ischemic necrosis.

Occurs very fast due to circulating antibodies

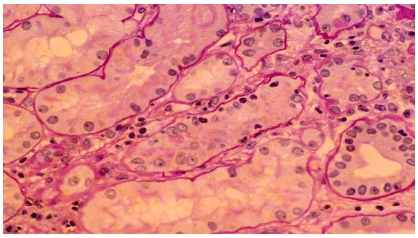


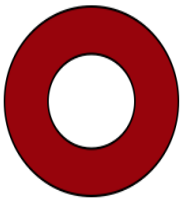
Normal

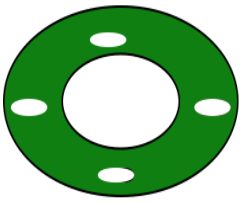


Subtotal **renal infarction** due to **hyperacute (antibody-mediated) rejection.**

Borderline Changes (Suspicious for acute rejection)







1-4 cells

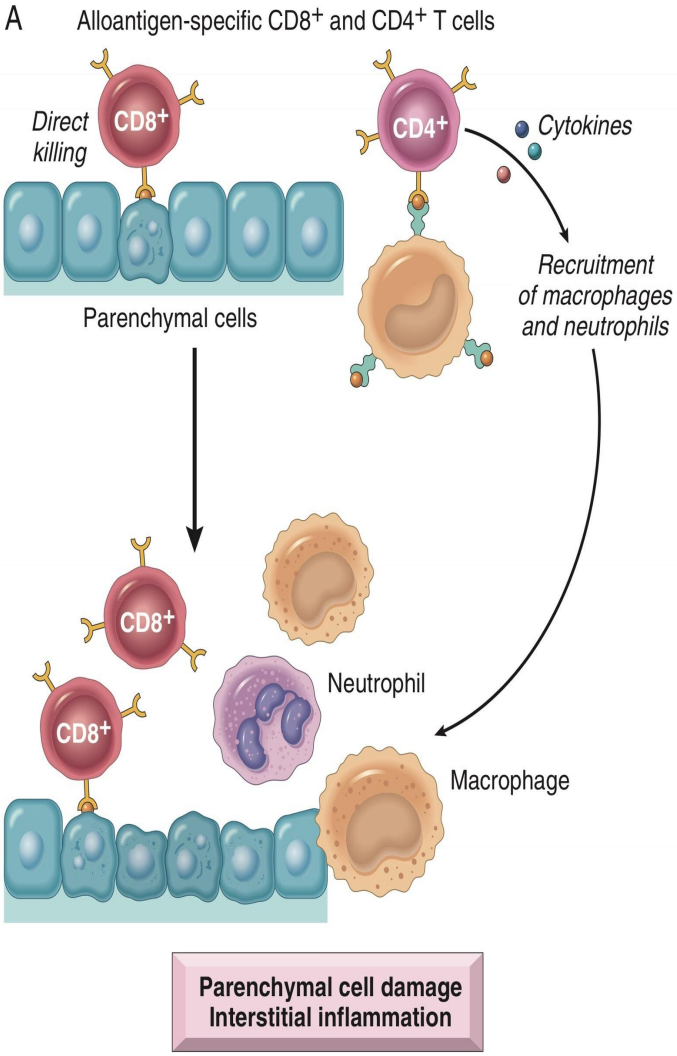
In this case we'll talk to the clinician to treat the patient:

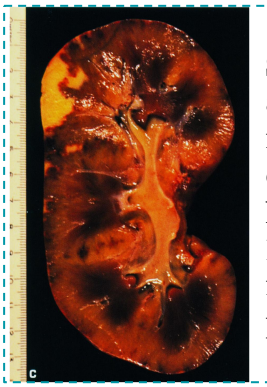
- If the creatinine is increased, we will treat him as it is an acute T-cell mediated rejection, give him (immunosuppressant), لأننا بالمجهر نشوف بس منطقة وحدة من مناطق كثيرة في الكلية اللي ممكن تكون (acute T-cell mediated rejection).
- If the creatinine is normal, we will wait.

Acute rejection (T-cell mediated)

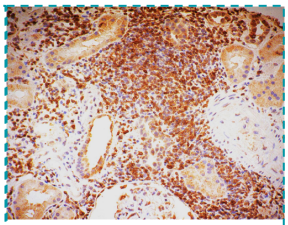
Acute rejection may occur within days to weeks and sometimes after months or years later. It can be due to either:

1. **cellular rejection** =>Most common, accompanied by clinical signs of renal failure. Histologically; shows extensive CD4+ & CD8+ T cell marked by edema and mild interstitial mononuclear (lymphocytes)hemorrhage Could lead to focal **tubular** necrosis, endarteritis , Parenchymal injury. we should take a biopsy to distinguish between rejection and drug toxicity Patient typically respond promptly to increase immunosuppressive therapy.
2. **humoral / vascular rejection** => associated with vasculitis.caused by antidoron antibodies Histologically; necrotizing vasculitis with **endothelial** cell necrosis, neutrophilic infiltration, deposing of antibodies, fibrin, thrombosis



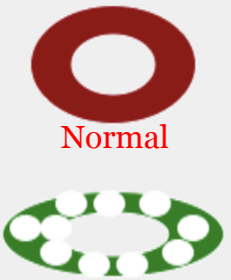
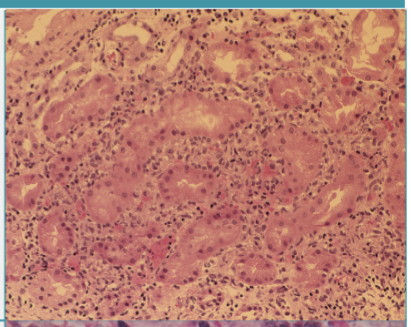
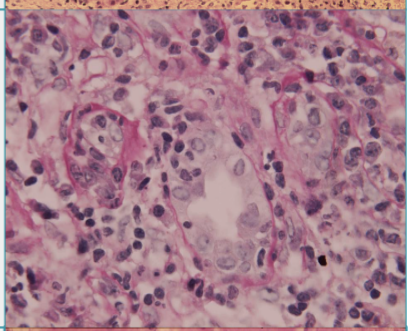
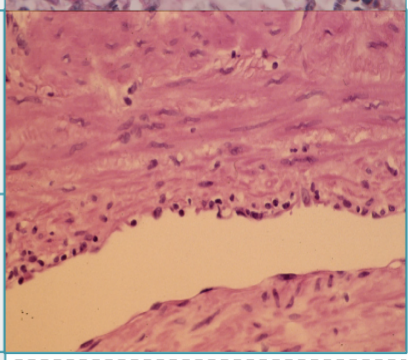
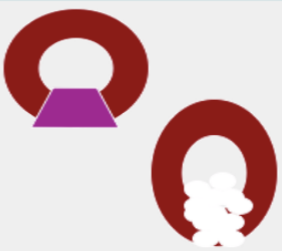


Severe acute rejection of donor kidney. Focal infarcts are present.



Acute rejection
The interstitial infiltrate consists of T cells mainly.

The Banff classification of acute rejection

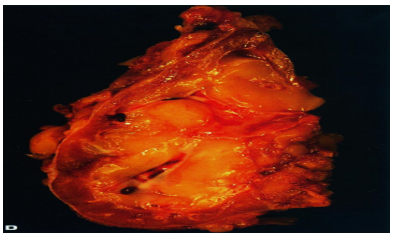
Grade I The blood vessels are normal	A	→ Mononuclear interstitial inflammation(>25 %). ✚ → Moderate tubulitis. (5 to 10)		
	B	→ Mononuclear interstitial inflammation(>25 %) ✚ → Severe tubulitis(>10)		
Grade II	A	→ Mild to Moderate intimal arteritis		
	B	→ Severe intimal arteritis[1]		
Grade III		→ Transmural[2] arteritis and/or fibrinoid necrosis. a finding termed endotheliitis or intimal arteritis.		

Notes: Important
-The more interstitial inflammation and the more tubulitis we have the higher the grade.
-Acute grade I&II are T cell mediated while Grade III can be T cell mediated or antibodies mediated rejection.

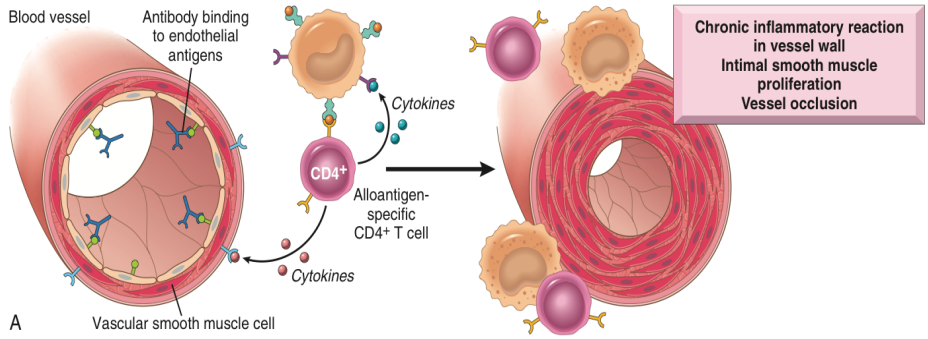
- (1) But not the whole wall.
- (2) occurring across the entire wall.
- In acute grade 3 antibody mediated rejection there's a marker C4D complement.

❖ Chronic Allograft Nephropathy:

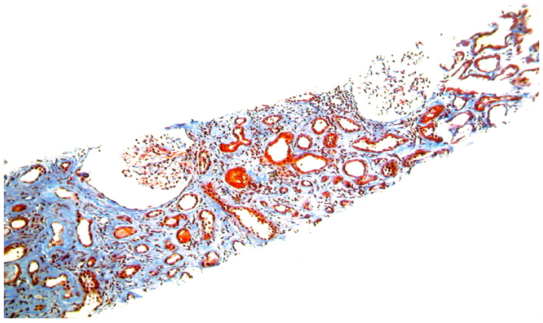
-Presents late after transplantation (**months to years**) with a progressive **rise in serum creatinine** levels. Chronic rejection is dominated by vascular changes, **interstitial fibrosis and loss of renal parenchyma,gradual narrowing of graft blood vessels graft arteriosclerosis**. Chronic rejection **<u>does not</u>** respond to standard immunosuppression treatment.(it means all the previous types they are respond)



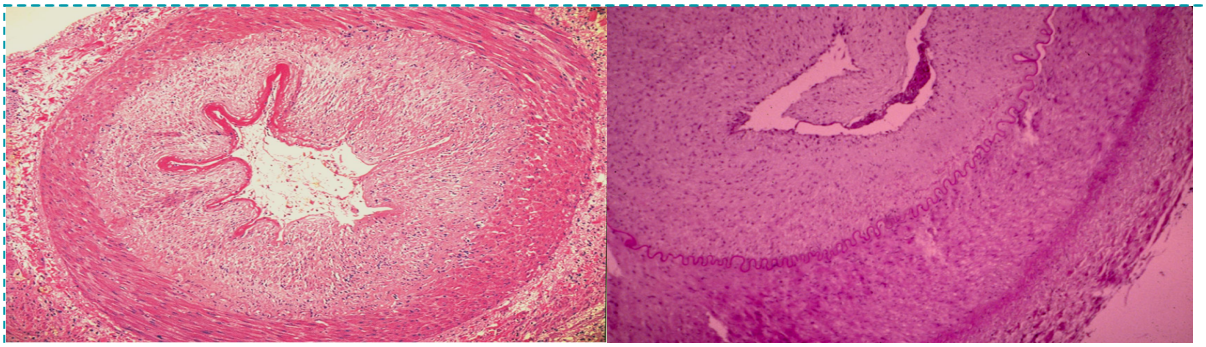
Severe chronic rejection. (graft arteriopathy). Note the severe parenchymal atrophy and the thick-walled arteries.



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



Chronic/ sclerosing allograft nephropathy or transplant arteriopathy.
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.



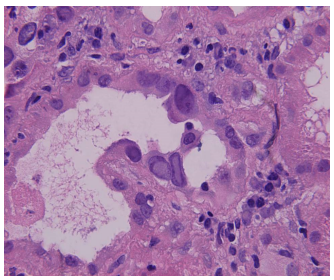
Chronic/ sclerosing allograft nephropathy.
The classical lesion of chronic transplant vasculopathy is a circumferential **proliferation of myointimal cells** with an **intact internal elastic lamina.**

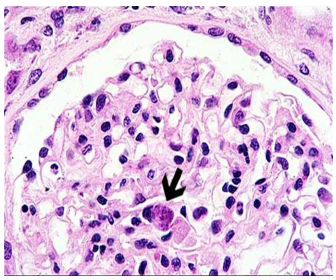
Treatment based on Banff classification

- Normal, Suspicious — **No Treatment**
- 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**

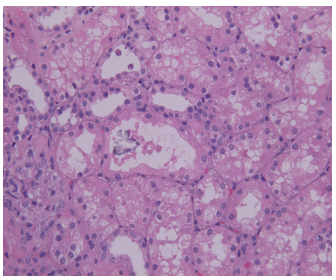
What are the outcomes of theses treatments?

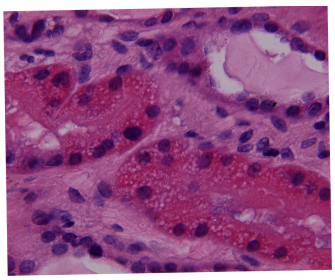
1-Infections : Recurrent or De Novo GN disease





2-Drug Toxicity



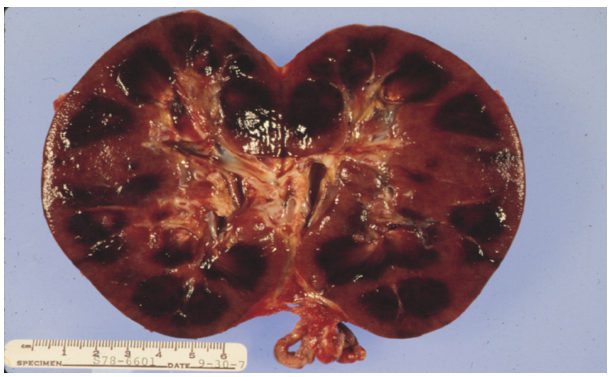


How you will stopping it?

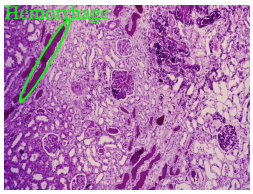
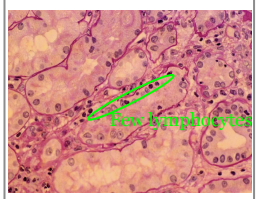
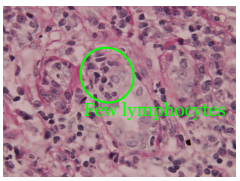
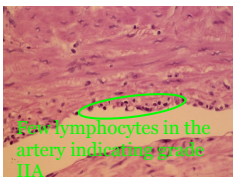
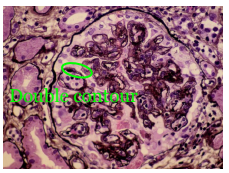
One strategy is to prevent host T cells from receiving costimulatory signals from donor DCs during the initial phase of sensitization. This can be accomplished by administration of agents that **block the interaction of the B7 molecules on the DCs of the graft and the CD28 receptor on host T cells**, which, by interrupting the second signal for T cell activation, induces either **T cell apoptosis or anergy.**

Conclusion

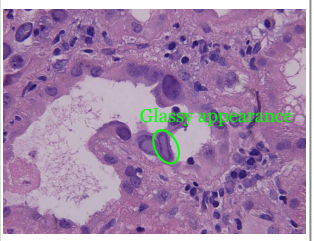
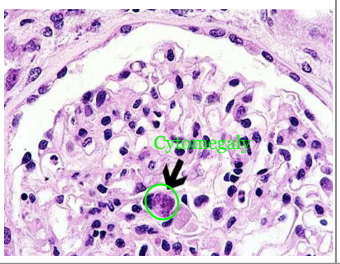
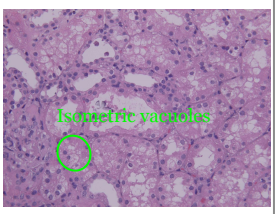
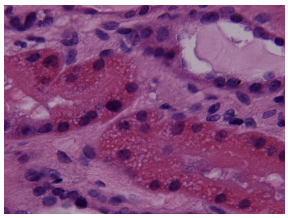
The Banff classification has proposed a schema for interpretation and gradation of the histological findings in renal allograft biopsies that can be used as an **indication** for therapeutic consequences and expected graft survival.



Histopathology Of Renal Transplantation

Condition	Hyperacute rejection	Borderline changes	Acute rejection Grade I	Acute rejection Grade IIA	Chronic Rejection
Picture					
Prominent Features	- Hemorrhage, fibrinoid necrosis - Vessel thrombosis - Later stage: polymorph infiltration within arterioles, glomeruli, and peritubular capillaries	Tubular interstitial inflammation (few lymphocytes) a little bit of tubulitis	- Mononuclear interstitial inflammation - Tubulitis	Mild to moderate intimal arteritis.	Important - Double contours(means double basement membrane) along glomerular capillary loops (Transplant glomerulopathy). - Interstitial fibrosis.
Notes	○ In acute rejection grade I you'll see moderate tubulitis in grade A, and severe tubulitis in grade B. ○ In acute rejection the interstitial infiltrate consists mainly of **T cells**. ○ In acute rejection grade IIB you'll see severe intimal arteritis (it will be filled with lymphocytes) ○ There is marked **tubular atrophy** in chronic rejection. ○ There is narrowing of lumen of vessels in chronic rejection caused by circumferential proliferation of myointimal cells with an intact internal elastic lamina. (In malignant hypertension there are layers of the elastic layer)				

Histopathology Of Renal Transplantation

Condition	Polyomavirus infection	Cytomegalovirus infection	Acute drug toxicity	Chronic drug toxicity
Picture				
Prominent Features	Important - Ground glassy appearance. - Nuclei.	- Increased cell size. - **Inflammatory infiltrate.**	Isometric vacuoles in tubular epithelial cells.	- Nodular hyaline in the wall of blood vessel. - Interstitial fibrosis.
Notes	○ Special stains are used for the investigation of polyomavirus infection. ○ **Polyomavirus** in **tubules(Distal mainly**, while **cytomegalovirus** can be **anywhere** (not specific) ○ Ischemia may cause isometric vacuoles as well so we should check the drug level in the blood to know the etiology whether it's ischemia or drug toxicity.			

SUMMARY

RECOGNITION AND REJECTION OF TRANSPLANTS

- Rejection of solid organ transplants 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 of solid organ grafts are as follows:
  - *Hyperacute rejection:* Preformed anti-donor 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 antibody-mediated (humoral) rejection:* Antibodies damage graft vasculature.
  - *Chronic rejection:* Dominated by arteriosclerosis, this type is caused by T cell activation and antibodies. The T cells may secrete cytokines that induce proliferation of vascular smooth muscle cells, and the antibodies cause endothelial injury. The vascular lesions and T cell reactions cause parenchymal fibrosis.
- Treatment of graft rejection relies on immunosuppressive drugs, which inhibit immune responses against the graft.
- Transplantation of hematopoietic stem cells (HSCs) requires careful matching of donor and recipient and is often complicated by graft-vs-host disease (GVHD) and immune deficiency.

1- A **cyanotic** kidney is a feature of?
A. Normal kidneys
B. Acute rejection
C. Chronic rejection
D. Hyperacute rejection

2- Which of the following is **T-cell mediated**?
A. Normal kidneys
B. Acute rejection
C. A&B
D. Hyperacute rejection

3- **Vasculitis** is associated with?
A. Normal kidneys
B. Acute rejection
C. Chronic rejection
D. Hyperacute rejection

4- We can see **mild intimal arteritis** in:
A. Grade IA
B. Grade IB
C. Grade IIA
D. Grade III

5- A patient had a successful renal transplant and in a **year** he bad routine check up that revealed progressively **high serum creatinine levels**. What could that be an indication of?
A. Normal kidneys
B. Acute rejection
C. Chronic rejection
D. Hyperacute rejection

Answers:
1-D
2-B
3-B
4-C
5-C

6- We can see **fibrinoid necrosis** in:
A. Grade IA
B. Borderline changes
C. Grade IIB
D. Grade III

7- Where can we see **double contour**?
A. Chronic allograft nephropathy
B. Amyloidosis
C. DDD
D. RPGN

8- Hyperacute rejection lead to?
A.Ischemic necrosis
B.Interstitial fibrosis
C.Endotheliitis
D.Atrophy

9- A patient had an infection after his kidney transplant. Histological picture shows **infiltration** throughout the glomeruli, tubules and interstitium, what infection could that be?
A. TB
B. Polyomavirus
C. Cytomegalovirus

10- A patient had an infection after his kidney transplant. Histological picture shows **ground glass** appearance, what infection could that be?
A. TB
B. Polyoma
C. Cytomegalovirus

11-An 18 year old female had a renal transplantation 1 year ago due to end-stage kidney disease with unknown etiology. Her serum creatinine was high. A renal biopsy was taken, showed **tubulointerstitial inflammation with lymphocytes.** What is the diagnosis?(important)

A) Acute antibody mediated rejection
B) Acute cellular rejection
C) Chronic rejection
D) Recurrence of original disease

Answers:
6- D
7- A
8- A
9- C
10- B
11-B

زميلاتي وزملائي أعضاء تيم الباثولوجي

نهنئكم على قرب انتهاء السنة الأولى مقدرين لكم جهودكم الرائعة والمخلصة لهذا التيم

تعاونكم سر نجاح التيم واحترامكم لأوقات تسليم المحاضرة وبذل أفضل مالديكم

نتفق معكم إنها تجربة بسيطة إلا أنها حسّنت وصقلت جوانب عديدة في شخصية كلاً منّا من أهمها آلتواصل ، العمل ضمن فريق ، احترام مواعيد التسليم والتميز المعرفي في المادة والكثير...

ونّود تبشيركم بوصول تغذية راجعة إيجابية للمحاضرات السابقة من قبل عدد كبير من الدفعة

شكراً لكم من القلب ووفقكم الله أينما كُنتُم ❤️

وتذكروا أن عملنا هذا سوف يترك أثراً جيداً للدفعات الأعوام القادمة بإذن الله ...

كما نود أن نشكر جميع من عمل في التيم من بداية السنة سواء قادة أو أعضاء فَلَولا توجيهاتكم ونصائحكم لم نصل إلى هنا.

كونوا بخير دائماً،،،

القادة

فاطمة بالشرف **عبدالله العمر**

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