

# Pathology of Renal Allograft

The lecture too easy but to cover it all and to enjoy with , study the immunology lecture .  
Our video in this amazing lecture is 'a patient undergoes a transplantation surgery' enjoy :

<https://youtu.be/qAjAHYhv4f8>  
Robotic transplantation

## 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.

## 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.

Index:  
Important  
NOTES  
Extra Information

# Kidney Transplant

- Patients with end-stage renal disease (ESRD) are treated with renal transplantation and dialysis.
- 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.

## Terminology

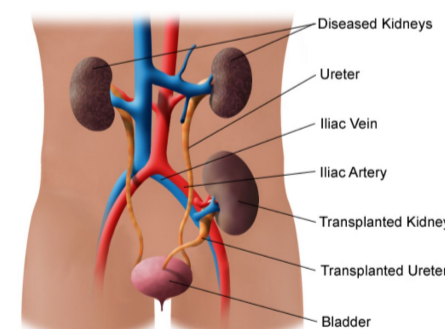
<b>donor kidney, allograft or graft</b>	The transplanted (new) kidney
<b>alloantigens</b>	The antigens present in the allograft kidney
<b>alloantibodies</b>	The antibodies that are against alloantigens (that target the alloantigens) are anti-allograft antibodies
<b>Donor</b>	The patient who donates kidney is called the
<b>recipient</b>	the patient who receives the new transplant kidney

- The donor kidney (Transplanted kidney) which is placed in the recipients iliac fossa or groin region.
- The ureter is inserted into the bladder.
- The blood vessels are anastomosed.

Extra from 438 : usually we do not remove the old kidney, unless it's in risk of infection

- The donor of the kidney could be living or deceased (dead)

Example of a Kidney Transplant



## Pathology of injury in kidney transplant

1- Harvest injury

2- Rejection: hyperacute, acute and chronic

3- Infections in the renal allograft

4- Drug toxicity, acute & chronic

5- Recurrence of primary disease

6- De-novo (new) disease

# 1- 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 donor death
- It can lead to non-functioning kidney immediately after transplant in which the patient will have anuria (non passage of urine)
- Harvest kidney usually recover with appropriate management.

# 2- 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.


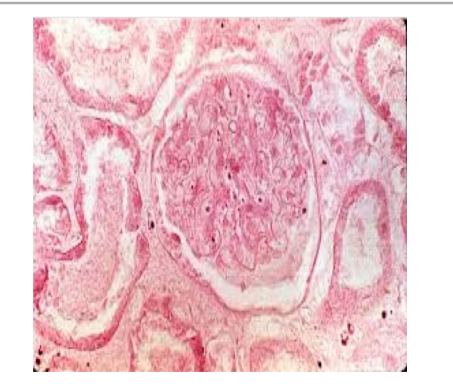
<b>Types of rejection</b>	a) Hyper-acute	b) Acute: 1-Acute T-cell mediated rejection. 2-Acute antibody mediated rejection	c) Chronic 1-Chronic T-cell mediated rejection. 2-Chronic antibody mediated rejection
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- Rejection has been classified by a system called as the Banff Classification

## a) Hyperacute rejection

هالنوع يصير لما شخص يخضع للعملية بس عنده previous AB كيف تكونو ممكن  
multiple blood transfusion or mlti pregnancy فلما تدخل الكلى الجديدة  
الجسم ، تروح هالـAB تهاجمه بسرعه

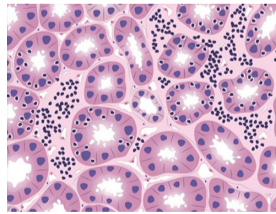
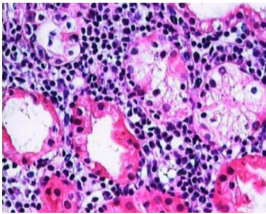
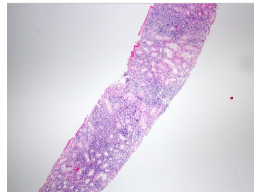
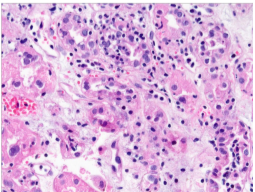
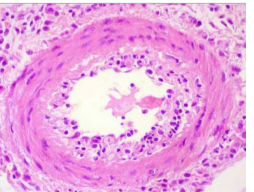
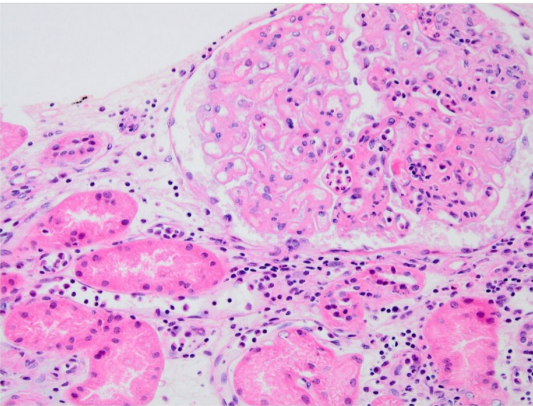
- Rare **in today's world**
- Rejection of the allograft occurring immediately after implantation and perfusion of graft.
- Occurs within minutes to hours after transplantation.

<b>Morphology</b>	Gross	<ul style="list-style-type: none"> <li>• Cyanosis of graft minutes to hours after perfusion</li> <li>• Graft becomes swollen, hemorrhagic, and necrotic</li> </ul>	
	Microscopic	<ul style="list-style-type: none"> <li>• Vasculitis, thrombosis, fibrinoid necrosis of blood vessels</li> <li>• Thrombi in glomeruli</li> <li>• Interstitial edema and hemorrhage</li> <li>• Infarct of the kidney (coagulative necrosis) and loss of graft</li> </ul>	

# b) Acute rejection

غالباً يكون T cell MR لان B cells تأخذ وقت عشان تكون الالانتيبيديز ضد الكلى الجديدة

- 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.

Types of acute rejection	Acute <b>T-cell mediated</b> rejection (acute <b>TCMR</b> )	Acute <b>antibody-mediated</b> rejection (acute <b>ABMR</b> )
<p><b>Overview</b></p>	<ul style="list-style-type: none"> <li>• Common form of rejection.</li> <li>• An acute immune reaction by the recipient against the antigens present in the allograft (alloantigens).</li> <li>• Mediated by T cells.</li> <li>• Classically it develops in the first 3 months after transplantation, but may erupt at any time, even after many years.</li> </ul>	<ul style="list-style-type: none"> <li>• Also called as acute humoral rejection.</li> <li>• An acute antibody mediated immune reaction.</li> <li>• Mediated by the anti-allograft antibodies (alloantibodies) called donor specific antibodies (DSA).</li> </ul> <p>(الفرق بينه وبين الHyperacute Rejection ان الAB تتكون بعد الزراعة)</p> <p>To sum up, what you need to know about pre-existing antidonor specific antibodies is that their presence will cause graft rejection</p>
<p><b>Characteristics</b></p>	<ul style="list-style-type: none"> <li>• There is infiltration of allograft by lymphocytes (mainly T-cells) and other inflammatory cells.</li> <li>• <b>The inflammation is primarily in the tubules (tubulitis) and the interstitium (together called tubulointerstitial inflammation) and may also involve the arteries called vasculitis/arteritis (not always present) (+/- fibrinoid necrosis of arteries).</b></li> <li>• Acute TCMR responds well to immunosuppressive drug therapy.</li> </ul>	<ul style="list-style-type: none"> <li>• The recipient already has pre-formed (i.e. present before transplantation) circulating anti-donor specific antibodies (DSA).</li> <li>• <b>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.</b></li> <li>• The microvasculature of the kidney (i.e. glomeruli and peritubular capillaries) is the main target.</li> </ul>
<p><b>Clinical features</b></p>	<p>Clinically there is loss of graft function and it presents as rising creatinine.</p>	
<p><b>Microscopy</b></p> <p><b>NOTE:</b> arteritis/vasculitis can be seen in <b>both</b> acute TCMR and acute ABMR.</p>	<ul style="list-style-type: none"> <li>• Tubulointerstitial inflammation (<b>T Lymphocytes seen</b>) with or without arteritis</li> <li>• Interstitial edema and sometimes hemorrhage.</li> </ul> <p>NOTE: glomerular usually not involved <b>unlike ABMR.</b></p> <div style="display: flex; justify-content: space-around;">   </div> <div style="display: flex; justify-content: space-around;">    </div> <p>Arteritis (vasculitis)</p>	<ul style="list-style-type: none"> <li>• Glomerulitis, capillaritis of the peritubular capillaries (peritubular capillaritis).</li> <li>• <b>Positive C4d immunostain</b> in the peritubular capillaries.</li> <li>• Acute tubular injury/ necrosis.</li> <li>• Arteritis +/- fibrinoid necrosis.</li> <li>• Acute thrombotic microangiopathy like picture</li> </ul>  <p>Glomerulitis &amp; peritubular capillaritis</p>



## a) chronic ejection

Chronic rejection is the type of rejection that happens over an extended period of time and can eventually lead to loss of the graft **if it wasn't treated properly**

<b>Characteristics</b>	<ul style="list-style-type: none"><li>• Persistent or recurrent episodes of TCMR or ABMR → chronic changes in allograft → chronic rejection (chronic TCMR and chronic ABMR) → end stage allograft kidney (graft loss).</li><li>• It does not respond to immunosuppressive therapy.</li></ul>
<b>Clinical features</b>	<ul style="list-style-type: none"><li>• <b>Gradual</b> rise in serum creatinine</li><li>• Patients presents with chronic graft dysfunction/ chronic renal failure</li><li>• Proteinuria</li><li>• Hypertension</li></ul>
<b>Morphology</b>	<b>Microscopy</b> <ul style="list-style-type: none"><li>• Tubulitis and tubular atrophy.</li><li>• Interstitial inflammation and fibrosis.</li><li>• Arteries show intimal fibrosis with chronic inflammation called chronic transplant arteriopathy.</li><li>• Glomeruli: global or focal segmental glomerulosclerosis</li><li>• Chronic ABMR also shows a unique type of glomerular injury called transplant glomerulopathy.</li></ul>

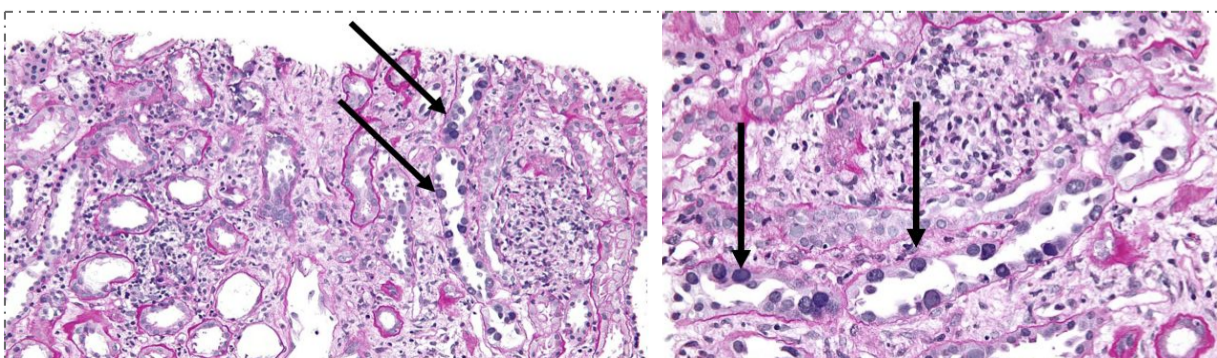
## 3- Infections of the renal allograft

The patients who are recipients of allograft kidney are given various immunosuppressive drugs are therefore immunosuppressed (immunocompromised).

These patients are predisposed to various renal infections like:

Polyomavirus (Sv40 virus)  
Adenovirus  
Cytomegalovirus  
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.
- These infections can lead to graft loss
- Infection with EBV can also lead to post transplant lymphoproliferative disorder (PTLD) (**develop lymphoma**)



**Renal tubules showing Polyomavirus infection in allograft kidney (arrows)**

## 4-Drug toxicity

**Calcineurin inhibitors (CNIs):** immunosuppressive drugs given to the recipient to decrease their immune system response to the transplanted kidney and therefore help suppress acute rejection.

Examples of CNIs: cyclosporine and tacrolimus

The problem is that CNIs are also nephrotoxic and can cause acute or chronic damage to the graft

Blood tests show:

- Rising serum creatinine
- Elevated levels of CNI in blood

They can cause acute CNI toxicity and chronic CNI toxicity in the kidney

### Acute CNI toxicity shows

- acute tubular injury
- isometric vacuolization of proximal tubule
- acute thrombotic microangiopathy like picture.

### Chronic CNI toxicity shows

- striped interstitial fibrosis
- tubular atrophy
- Microcalcifications
- nodular arteriolar hyalinosis
- chronic thrombotic microangiopathy like picture.

## 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

# Quiz

**1-a patient who had a transplanted kidney died immediately after surgery , a renal biopsy is done to detect the cause of death , the results showed Interstitial edema and hemorrhage , coagulative necrosis and thrombosis in glomerulus . What is the cause of death ?**

- |                              |                         |                    |                      |
|------------------------------|-------------------------|--------------------|----------------------|
| a- not related to the kidney | b- hyperacute rejection | c- Acute rejection | d- Chronic rejection |
|------------------------------|-------------------------|--------------------|----------------------|

**2-60-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-Tubular atrophy and interstitial fibrosis | c-Neutrophilic vasculitis and fibrinoid necrosis | d-Interstitial infiltrates of lymphocytes and macrophages |
|---|---|--|---|

**3- A patient who had a transplant 2 months ago is now having rising creatinine, biopsy is done showing Glomerulitis and capillaritis, CD4 stain is positive. What is your diagnosis?**

- |                         |         |         |                      |
|-------------------------|---------|---------|----------------------|
| a- Hyperacute rejection | b- TCMR | c- ABMR | d- Chronic Rejection |
|-------------------------|---------|---------|----------------------|

**4-patient present in the hospital received a kidney transplant 2 days later , the examination before the discharging of patient shows rises creatinine and the microscopic examination showed tubulointerstitial inflammation and normal glomerulus , what do you the diagnosis?**

- |         |         |                                     |                         |
|---------|---------|-------------------------------------|-------------------------|
| a- ABMR | b- TCMR | c- immunosuppressive drugs toxicity | d- hyperacute rejection |
|---------|---------|-------------------------------------|-------------------------|

**5-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-performed AB | b-T helper cells | c-Mononuclear phagocytes | d-macrophages |
|----------------|------------------|--------------------------|---------------|

**Answers:**

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

# Summary

## Harvest injury

- ❖ **Tubular injury** to the transplanted allograft kidney, due to cold ischemia time or the mode of donor death.
- ❖ It can lead to **non-functioning** kidney immediately after engraftment in which the patient will have **anuria**.
- ❖ usually **recover**.

Rejection is a **major** complication seen **post-transplantation**

## Types of Rejection:

Hyperacute rejection	Acute rejection	Chronic rejection
<ul style="list-style-type: none"> <li>❖ <b>Immediately</b>.</li> <li>❖ <b>Minutes</b> to <b>hours</b> after transplantation.</li> </ul>	<ul style="list-style-type: none"> <li>❖ The <b>most common type</b> of rejection.</li> <li>❖ <b>Days</b> or <b>the first few months after surgery</b>. Sometimes it can occur after years.</li> </ul>	<ul style="list-style-type: none"> <li>❖ Usually occurs <b>after</b> the <b>first year</b> of transplantation.</li> <li>❖ Lead to loss of the graft.</li> <li>❖ Doesn't respond to immunosuppressive therapy.</li> </ul>

## Infection Of The Renal Allograft

- ❖ The renal allograft immunosuppressed & 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**.
- ❖ Blood test show:
  - Elevated of serum creatinine.
  - Elevated blood/ serum CNI levels.

## Recurrence of primary disease

- ❖ The primary disease which lead to **end stage kidney**.
- ❖ It is not very common.

## De-novo (new) disease / glomerulonephritis

- ❖ It is the development of another kidney disease in the renal allograft.
- ❖ It is very rare.



## We Are Done

بحمد الله ومنتته أنهينا سنتنا الأولى ، ونود حقيقةً شكرَ جميع من شارك في هذا العمل

so proud of you and we really appreciate that .

مقدرين لكم جهودكم الرائعة والمخلصة لهذا التيم ، تعلمنا الكثير خلال هذه الرحلة برفقتكم ، وكل

رحلة لا تخلو من العقبات والصعوبات في بادئ الأمر ، ولكن لم تكن عائقًا بل صقلنا بها نقاط

ضعفنا ، لنصل لما نحن عليه الآن ونعدكم بالأفضل بإذن الله تعالى.

وفقكم الله لما يحب ويرضى .

- فاطمة آل هلال البندري العنزي منى العبدلي ريناد الحميدي غادة العبدلي نورة السالم نورة الكثيري ساره العبيد لمى الأحمدى الجوهرة البنيان غيداء العسيري ساره المقاطي غادة العثمان مريم الرحيمي دعاء غيداء المرشود غادة السويلم فرح السيد ، غادة العبدلي ، هيا العنزي ، نوره الدهش ، لينا المزيد
- أحمد الحوامدة ، عبدالرحمان الدويش يزيد القحطاني حمد موسى عبدالعزيز الربيعة ابراهيم التميمي عبدالعزيز السحيم فيصل الفضل عبدالرحمن بارشيد ناصر السنبل أحمد خواشكي محمد الوهيبي بندر الحربي ، احمد الخياط ، بسام الأحمري ، خالد القبلان ، عمر الحبلي

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