PATHOLOGY TEAM 436

MEDICINE
KING SAUD UNIVERSITY

Urinary tract infection

Revised by
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Objectives:

1. Recognize the predisposing factors for infections of the kidney and urinary tract.

2. Describe the different types of infections in the kidney and urinary tract.

3. Recognize the clinicopathological features of acute and chronic pyelonephritis.

4. Describe the causes of urinary tract obstruction.

5. Recognize drug induced nephritis.

Black: Doctor's slides.

Red: important!

Green: Doctor's notes.

Grey: Extra.

Purple: Female's slides.

Blue: Male's slides.

Introduction: Urinary Tract Obstruction:

This obstruction may occur anywhere in the urinary system.

In children	In adults
Most often due to congenital malformations (associated with reflux or other causes).	Most often acquired and usually occurring as a consequence of renal stones or benign prostatic hyperplasia.

In Chronic: lymphocytes, fibrosis and scarring.
In Acute: neutrophils and polymorphs leukocytes.

- Clinical manifestations include:

1. Renal colic, which is an excruciating[1] pain caused by acute distention[2] of the ureter, usually due to the transit (movement) of a stone.
2. Hydronephrosis, which is a progressive dilation of the renal pelvis and calyces.
3. Infection, which is localized proximal to the site of obstruction and may lead to infection of the renal parenchyma.

- Upper Urinary tract: Pyelonephritis: a) Acute. b) Chronic.

- Lower Urinary tract: a) Ureteritis. B) cystitis. C) urethritis.

- UTI symptoms: High fever , shivers "in upper UTI" , the bacteria may go to the blood circulation and cause septicemia.
- UTI don't come like other infections (sore throat or others) there are factors in the body which are predisposing this person to have UTI.

1- Upper urinary infection > what happens in the kidney (pyelonephritis mainly).

2- Lower urinary infection > ureter = no.1 in the body that doesn't get any pathology.

- Glomerulus is resistant to infection mainly the infection in the tubules. So at the first stage infection will affect tubules – pelvis – calyces, and later on the glomerulus.
- **For girls**: we allow one infection because their anatomy predisposed to infection. **For boys**: we don't allow any infection. Start investigation immediately because it could be congenital defect.

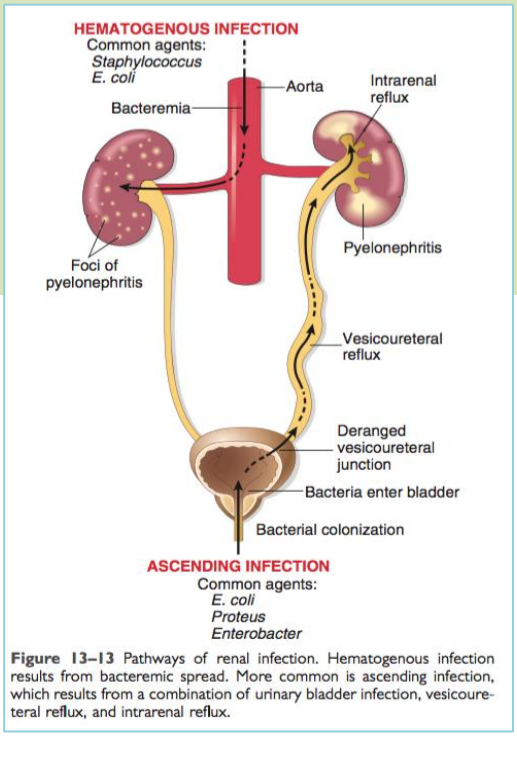


Figure 13–13 Pathways of renal infection. Hematogenous infection results from bacteremic spread. More common is ascending infection, which results from a combination of urinary bladder infection, vesicoureteral reflux, and intrarenal reflux.

Pyelonephritis[3]:

One of the most common diseases of the kidney and is defined as inflammation affecting the tubules, interstitium, and renal pelvis.

[1] Painful, intense.
[2] Swelling.
[3] Pyelo - means pelvis. Nephritis - inflammation in nephron.

- Routes of infection (Pathogenesis):

1- Ascending[4] infection: (most common) from the genital area

More than 85% of cases of urinary tract infection are caused by the gram-negative bacilli (***E. coli*** is by far the most common) that are normal inhabitants of the intestinal tract.

2- Hematogenous infection: e.g. TB, septicemia

What happens?

- ✓ Adhesion of bacteria to mucosal surfaces is followed by colonization of the distal urethra.
- ✓ The organisms then reach the bladder, moving against the flow of urine.
- ✓ Outflow obstruction or bladder dysfunction setts the stage for UTI.
- ✓ Bacteria then multiply undisturbed, without being flushed out or destroyed by the bladder wall.
- ✓ From the contaminated bladder urine, the bacteria ascend along the ureters to infect the renal pelvis and parenchyma.

- Predisposing factors of acute pyelonephritis:

1. Urinary tract obstruction, either congenital or acquired (stasis allowing bacteria to multiply a lot easier).
2. Instrumentation of the urinary tract (e.g. catheterization).
3. Vesicoureteral reflux[5]:
    - Young children with UTI, usually as a consequence of a congenital defect.
    - Acquired in persons with a flaccid[6] bladder resulting from spinal cord injury or with neurogenic bladder dysfunction secondary to diabetes.
4. Pregnancy (hormonal and mechanical changes increase the risk of urinary stasis and vesicoureteral reflux). Because there's a foreign body in the uterus the immune system will be more tolerant
5. Gender and age (Females are commonly infected due to the anatomy of UT 'nearer to GIT → microorganisms')
    - With increasing age the incidence in males rises as a result of prostatic hypertrophy and instrumentation.
6. Preexisting renal lesions, causing intrarenal scarring and obstruction.
7. Diabetes mellitus (predisposing factor for infection and bladder dysfunction).
8. Immunosuppression and immunodeficiency.

[4] Comes from the genital area mainly.
[5] retrograde flow of urine from the bladder to the kidneys.
[6] Flappy, loose.

- Clinical features:

The onset of uncomplicated acute pyelonephritis usually is sudden, with:

a) Flank pain. B) Systemic evidence of infection: fever, chills and malaise.

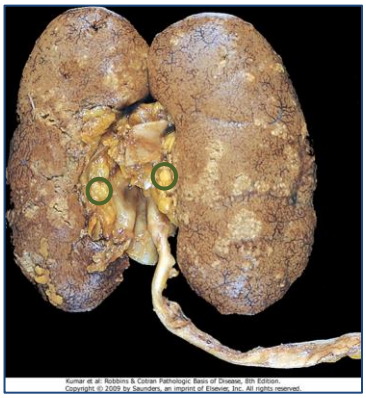
c) Dysuria, frequency and urgency. D) Pyuria, the urine appears cloudy due to the appearance of pus.

e) Leukocytosis, urinary white cells, and white cells casts in the urine (this latter finder is pathognomonic of acute pyelonephritis).

f) Usually unilateral.

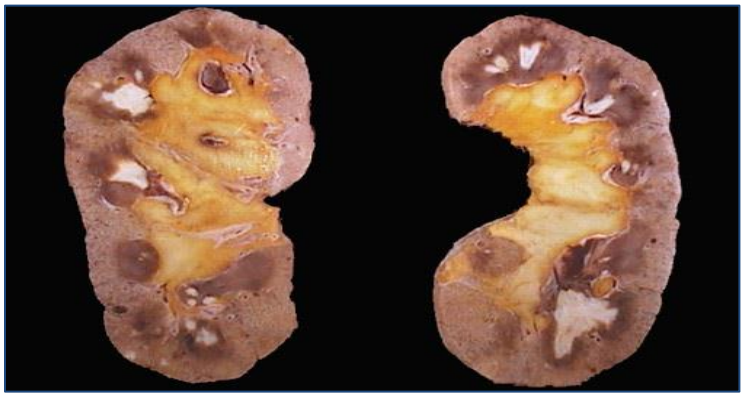
- Morphology: Very Important

إذا شفنا: Polymorphs + scar = acute in chronic



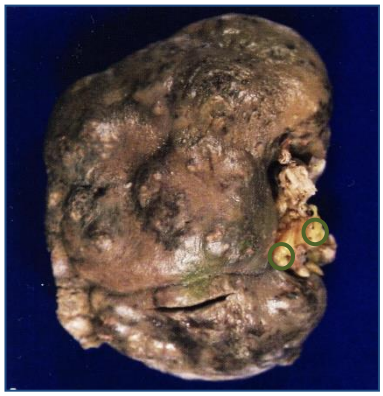
Acute pyelonephritis

Cortical surface shows grayish white areas of inflammation and abscess formation. O = collection of polymorph.

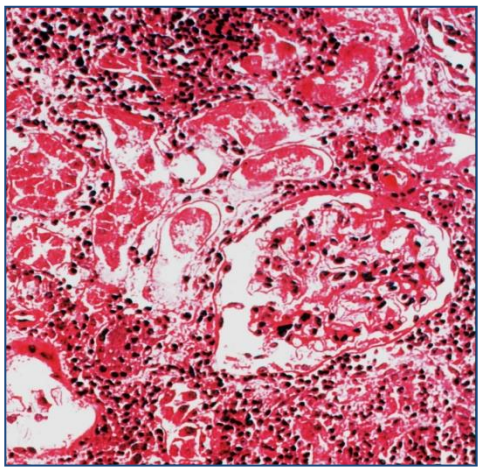


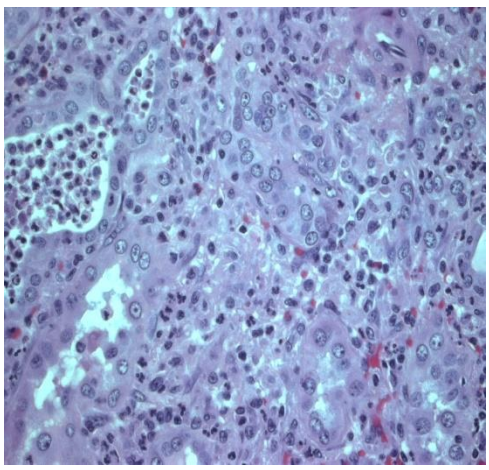
The pale white areas involving some or all of many renal papillae are areas of papillary necrosis.

This is an uncommon but severe complication of acute pyelonephritis, particularly in persons with diabetes mellitus. Papillary necrosis may also accompany analgesic nephropathy.



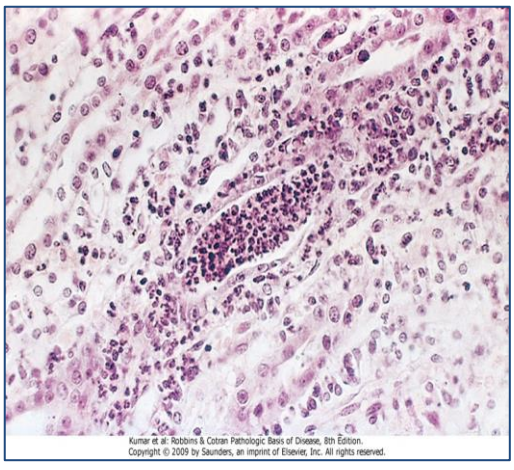
Acute on chronic pyelonephritis With numerous septic foci present in an already scarred kidney. We see neutrophils , lymphocytes and fibrosis.





Acute pyelonephritis:

There is a diffuse interstitial infiltrate with polymorphonuclear leukocytes (neutrophils).



Acute neutrophilic exudat (microbes) within tubules and interstitium inflammation (showing the characteristic white cell casts)

- Complications of acute Pyelonephritis:

1- Papillary necrosis.

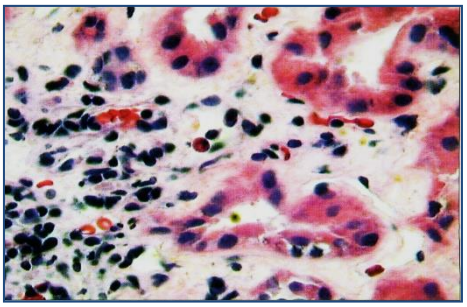
2- Pyonephrosis (pus inside the kidney).

3- Perinephric abscess (pus around the kidney "retroperitoneal cavity").

Tubulointerstitial nephritis:

Not an infection. It is due to some allergic reaction. And it affects the whole urinary tract.

- This group of diseases generally involve **inflammatory injuries** of the tubules and/or the interstitium of the kidney resulting in decreased renal function.
- It is often insidious in onset and principally manifest by azotemia
- Common causes include infection and drugs (analgesics such as NSAID or antimicrobials such as penicillin and methicillin)



Higher power of tubulitis demonstrating interstitial edema and invasion of the tubular epithelium by lymphocytes.

- Renal papillary necrosis:

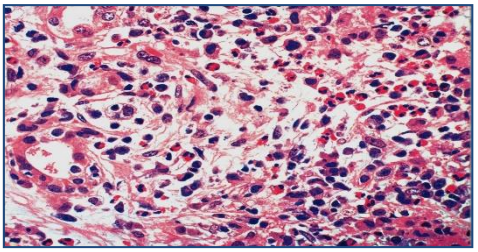
a) Ischemic necrosis of the tips of the renal papillae.

b) Chronic form.

c) Usually associated with long term persistent abuse of phenacetin (pain-relieving and fever-reducing drug)

This can lead to chronic analgesic nephritis, a chronic inflammatory change characterized by loss and atrophy of tubules and interstitial fibrosis and inflammation.

d) Usually associated with diabetes mellitus.



The mononuclear infiltrate is accompanied by abundant eosinophils and may have a granulomatous appearance.

- Acute drug induced interstitial nephritis:

Acute drug-induced tubulointerstitial nephritis (TIN) occurs as an adverse reaction to any of an increasing number of drugs. Acute drug-induced TIN is associated most frequently with synthetic penicillins (methicillin, ampicillin), rifampin, diuretics, NSAIDs, and numerous other drugs (phenindione, cimetidine).

a) Acute form, of immune etiology.

b) Usually triggered by penicillin derivatives or NSAIDs & diuretics.

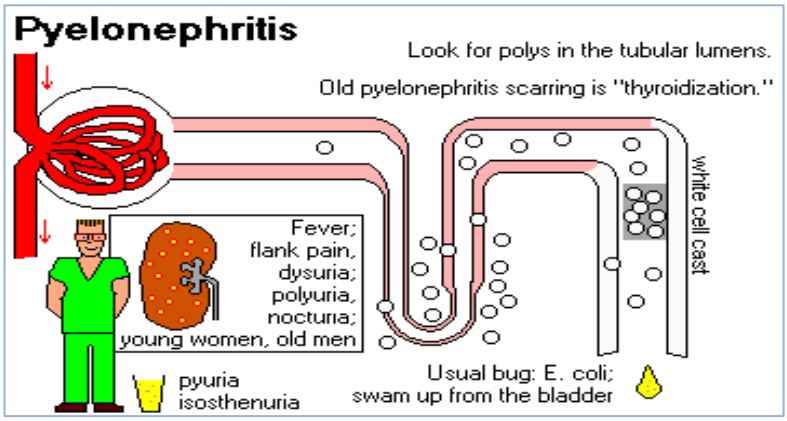
c) Eosinophils are characteristic.

d) Resolves on cessation of the inciting drug.

Microscopically we'll see eosinophils and granuloma due to the destruction of the tubules with neutrophils if it's acute.

- Pathogenesis:

- Serum IgE levels are increased in some persons, suggesting type I hypersensitivity.
- In other cases the nature of the inflammatory infiltrate and the presence of positive skin tests to drugs suggest a T cell–mediated (type IV) hypersensitivity reaction.



- Morphology:

- The abnormalities in acute drug-induced nephritis are in the interstitium.
- With some drugs (e.g., methicillin, thiazides, rifampin), interstitial non-necrotizing granulomas with giant cells may be seen.
- The glomeruli are normal except in some cases caused by nonsteroidal anti-inflammatory agents, in which the hypersensitivity reaction also leads to podocyte foot process effacement (the shortening, or thinning, of a tissue) and the nephrotic syndrome[7].

Chronic pyelonephritis:

- Chronic pyelonephritis is a disorder in which interstitial inflammation (at the beginning) and scarring (later) involve in the calyces and pelvis.
- Patients may have an underlying cause that predisposes them to having repeated bouts of acute pyelonephritis; which may progress to chronic pyelonephritis.
- It is an important cause of *chronic renal failure.*
- Causes almost always include chronic urinary tract obstruction and repeated bouts (attacks) of acute inflammation. Consequences include renal hypertension and end-stage renal disease.

It is divided into two forms:

1) Chronic Reflux-Associated pyelonephritis (reflux nephropathy):

- When the chronic pyelonephritis is caused by a **vesicoureteric reflux**[8] or **intrarenal reflux**, it is called reflux nephropathy.
- It's the most common form of chronic pyelonephritis. It could be *unilateral* or *bilateral,* & it may result in one kidney scarring and atrophy or both, leading to renal insufficiency.

[7] Nephritic syndrome (or acute nephritic syndrome)is a syndrome comprising signs of nephritis, which is kidney disease involving inflammation. It often occurs in glomerulonephritis, which is characterized by a thin glomerular basement membrane and small pores in the podocytes of the glomerulus, large enough to permit proteins and red blood cells to pass into the urine (yielding proteinuria and hematuria). By contrast, nephrotic syndrome is characterized by only proteins moving into the urine. Nephritic syndrome, like nephrotic syndrome, may involve hypoalbuminemia due to the protein albumin moving from the blood to the urine

[8] flow of urine from the bladder back into the ureters can cause kidney infection.

2) Chronic Obstructive pyelonephritis:

- Pathogenesis:
    1. Obstruction → leads to stagnation→ predispose infection.
    2. Recurrent infection → leads to recurrent bouts of renal inflammation and scarring.

The disease can be *bilateral*, as with congenital anomalies of the urethra or *unilateral* ex: calculi (stones), obstructive lesions of ureter.

- Chronic Pyelonephritis - gross: ***Scarring** & ***fibrosis*** of the kidney.

*The fibrosis involves the capillaries of the glomeruli → ***glomerular sclerosis***.

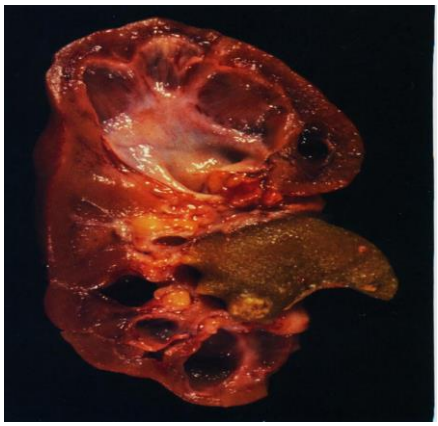
* If bilateral, the involvement is ***asymmetric***[9].

The hallmarks of chronic pyelonephritis are **coarse, discrete, corticomedullary scars** overlying dilated, blunted, or deformed calyces, and **flattening of the papillae.** This contrasts with chronic glomerulonephritis, in which both kidneys are diffusely and symmetrically scarred.

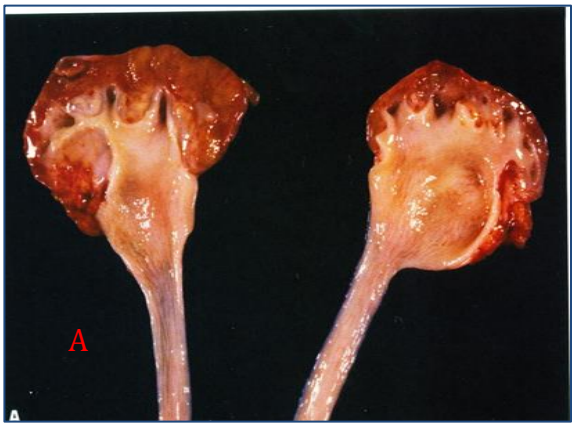
Renal tuberculosis

Renal tuberculosis secondary to hematogenous spread of tubercle bacilli. Caseating necrosis &Granuloma

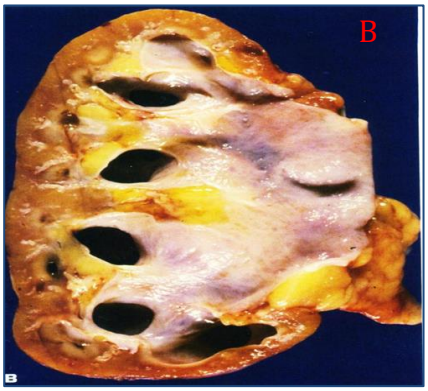
Staghorn calculus



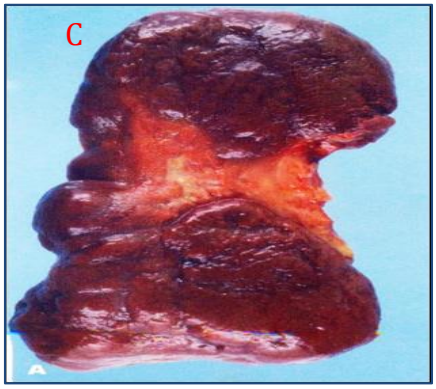
- **Staghorn** calculus in pelviureteric junction.
- Obstruction which causes stagnation then infection.



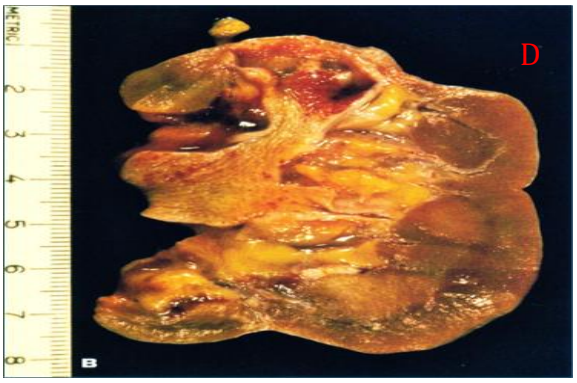
A. Bilateral hydronephrosis : its pressing and causing dilatation of pelvis and calyces due to Obstruction with acute on chronic pyelonephritis in a child due to urinary tract obstruction.



B. Hydronephrosis with thinned renal parenchyma in an adult kidney.

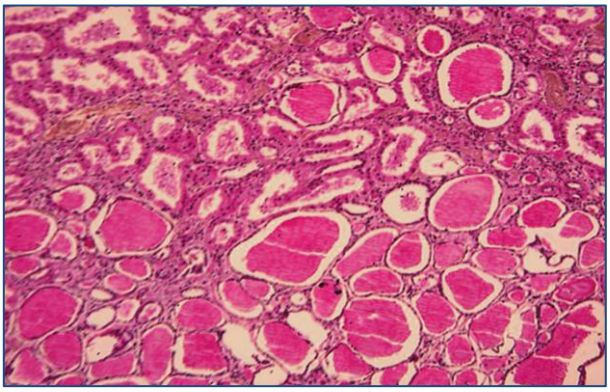


C. unshaped Scar of healed pyelonephritis.

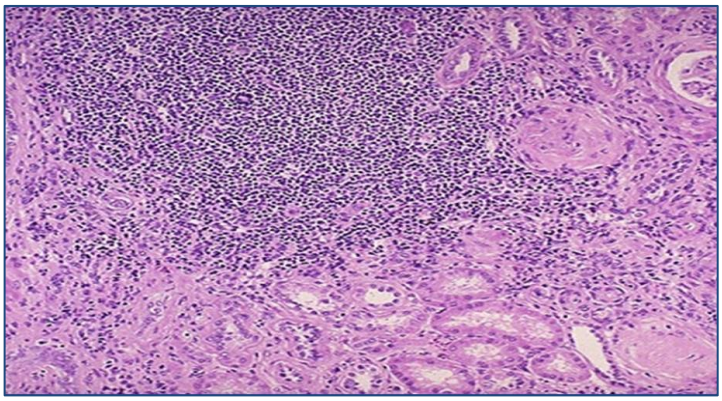


D. Healed pyelonephritis associated with vesicoureteral reflux has produced scarring of both poles of the kidney with calyceal distortion due to infection of the peripheral compound papillae.

[9] The areas involved in both kidneys are not identical.



Thyroidization of the kidney occurs due to chronic pyelonephritis (Eosinophilic proteinaceous casts).



Collection of chronic inflammatory cells here is in a patient with a history of multiple recurrent UTI. Both lymphocytes and plasma cells are seen in this case. However, the plasma cells are most characteristic

- TIN consists of inflammatory disease primarily involving the renal tubules and interstitium.
- *Acute pyelonephritis* is a bacterial infection caused either by ascending infection because of reflux, obstruction, or other abnormality of the urinary tract, or by hematogenous spread of bacteria; characterized by abscess formation in the kidneys, sometimes with papillary necrosis.
- *Chronic pyelonephritis* usually is associated with urinary obstruction or reflux; results in scarring of the involved kidney, and gradual renal insufficiency. Specific type of pyelonephritis :
  1- **Could be related to TB** – caseating granuloma and multinucleated giant cells.
  2- Related to intracellular bacteria or other kind of bacteria giving us staghorn.
  3- Or extracellular bacteria giving us xanthogranulomatous = foamy histiocytes and granuloma.
- *Drug-induced interstitial nephritis* is an IgE- and T cell– mediated immune reaction to a drug; characterized by interstitial inflammation, often with abundant eosinophils, and edema.

- Drug related: a) Acute. B) Chronic.

- What cells do we see? A) Eosinophils. B)Plasma cells. C) Granuloma (More in chronic).

- Clinically: 1- Increase in serum creatinine and urea. 2- Acute kidney injury.

- What type of intrarenal lesion could lead to AKI? 1- Acute tubular necrosis.

2- Acute tubulointerstitial nephritis. 3- Acute vasculitis. 4- Crescentic Glomerulonephritis.

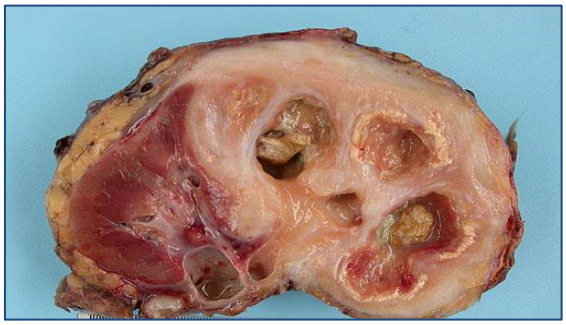
Chronic pyelonephritis: (Keywords) from Pathoma

A. Interstitial fibrosis and atrophy of tubules due to multiple bouts of acute pyelonephritis

B. Due to vesicoureteral reflux (children) or obstruction (e.g., BPH or cervical carcinoma)

C. Leads to cortical scarring with blunted calyces; scarring at upper and lower poles is characteristic of vesicoureteral reflux.

Urolithiasis:



Destruction of approximately 70% of the kidney. Numerous dilated calyces with yellow-brown calculi. The central necrotic areas are surrounded by dense fibrosis.

This condition is characterized by the formation of calculi (stones) in the urinary tract. The incidence is increased in men. Mostly unilateral.

- Symptoms:

1- Pain in the lower back part or in the lower abdomen "**flank pain**", which might move to the groin[10]. Pain may last from hours to minutes.

2- Nausea, vomiting.

3- Hematuria[11].

4- Burning during urination (dysuria), foul smell in urine, chills, weakness and fevers for urinary tract infection. (Predisposing factor of infection due to blood stasis).

- Types of stones in urinary tract: **1) Calcium stones[12]:**

- CALCIUM OXALATE and PHOSPHATE (70%). (Either one or both), they are formed in alkaline urine.
- They are radiopaque (can be seen by using x-rays).
- They are associated with **hypercalciuria** , which is caused by:

A) Increased intestinal absorption of calcium.

B) Increased primary renal excretion of calcium.

C) **Hypercalcemia**, which may be caused by:

(1) **Hyperparathyroidism** leads to **nephrocalcinosis[13]**, as well as urolithiasis.

(2) **Malignancy** leads to hypercalcemia because of osteolytic metastases or ectopic production of parathyroid hormone (often by squamous cell carcinoma of the lung).

Other causes include Vitamin D intoxication[14], sarcoidosis[15] and the milk-alkali syndrome[16].

Some people they have genetic abnormalities in liver (the liver produces oxalates which will be transported to the kidney) these patients may suffer from ESKD[17] and to cure them we have to make transplantation of liver and kidney.

---

[10] فخذ

[11] The presence of blood in urine.

[12] Also seen with Chorhn's disease (inflammatory bowel disease associated with formation of calcium oxalate).

[13] Calcification of the kidney.

[14] The active form of vitamin D responsible for increasing intestinal absorption of calcium.

[15] It is a multisystem inflammatory disease of unknown etiology that manifests as noncaseating granulomas, also one of its manifestations is to increase the production of active form of vitamin D which will lead to hypocalcaemia as we mention before.

[16] Characterized by high blood calcium caused by taking in too much calcium and absorbable alkali.

[17] End stage kidney disease.

2) Ammonium magnesium phosphate stones are the second most common form of urinary stones:

Magnesium ammonium phosphate. It is also, called infective stone. (15-20%) - (Struvite stone).

These stones are formed in alkaline urine, which is caused most often by ammonia producing or "splitting" (urease-positive) organisms, such as proteus vulgaris or staphylococcus.

infection by (urease-positive) organisms which split urea by its enzymatic effect to ammonia (basic molecule) which leads to increase the PH in urine ,the alkaline urine resulting in favorable conditions for the formation of stones by convert the soluble form of Mg and PO4 into insoluble form.

- They are radiolucent But if they were mixed with calcium phosphate, they become radiopaque.
- They can form large staghorn (struvite) calculi. (Staghorn calculi are renal calculi that obtain their characteristic shape by forming a cast of the renal -pelvis and calyces- تأخذ شكلها).

3) URIC ACID & URATE (5-10%).

Uric acid stones are associated with **hyperuricemia** in approximately half of the patients; hyperuricemia can be secondary to **gout** 'it could be due to increase protein intake' or to increased cellular turnover[18], as in the leukemias or myeloproliferative syndromes, they are radiolucent and form in acidic urine.

4) Cysteine[19] stone: They are almost always associated with **cystinuria[20]** or genetically determined **aminoaciduria,** they may form staghorn calculi, they are radiopaque and formed in acidic urine because they are acidic stones.

*One of the **risk factor** is high concentration of solute in the urinary filtrate and low urine volume (it could be due to either decrease water intake of increase water execration).

Urolithiasis: (Keywords)
Hematuria, unilateral, flank tenderness.
*Syndromes associated with each type of stones.
*Types of the stone, either radiopaque or radiolucent.

Cystitis[21]:

It's the finding of microorganism in the bladder with or without[22] clinical symptoms and with or without renal disease.

Significant bacteriuria: the number of bacteria in the voided urine exceeds the number that can be expected from contamination (i.e. ≥ 10^5 cfu/ml).

[18] Cell turnover means proliferation and apoptosis (the degradation of the cells will lead to produce purine base which is metabolized into uric acid).
[19] Type of amino acids.
[20] A genetic defect of tubules that results in decreased reabsorption of cysteine.
[21] Lower urinary tract infections
[22] Like in pregnant women.

- Clinical features:

1) Frequency[23]. 2) Urgency[24]. 3)Dysuria[25]. 4) Supra-pubic pain

5) Cloudy or foul-smelling urine. 6) Characteristic include pyuria[26] and often hematuria[27] but urinary white cell cast are not found.

There's a specific type of cystitis where you have a thinking of the muscular wall of the bladder.

- Etiology:

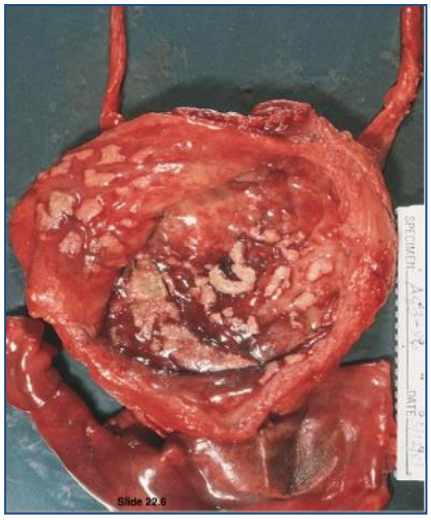
- Women are more likely to develop cystitis due to ***short urethral*** **distance.**
- Tuberculous cystitis is always a sequel to **renal TB**.
- **Candida albicans.**
- Schistosomiasis (Schistosoma haematobium)*. Usually associated with squamous cell carcinoma and autoimmune diseases.
- **Chlamydia** and **Mycoplasma** may also cause cystitis. Sexually transmitted
- Predisposing factors include bladder calculi[28], urinary obstruction, diabetes mellitus, instrumentation[29], and immune deficiency.
- Finally, irradiation of the bladder region gives rise to radiation cystitis.

*Whenever you have a patient especially male coming from the south PLEASE check his blood to cancel Schistosoma because it is usually associated with urinary Schistosomiasis.. You can get it by swimming, remember عبدالحليم حافظ مات بسببها لأنه كان يسبح بنهر النيل

Cystitis with Malakoplakia[30]:

We don't know the organism but it's intracellular so we can't culture it.

Peculiar[31] inflammatory reaction characterized by *soft, yellow, plaques* 3-4 cm in diameter. Most commonly occurs in the *bladder* and results from *defects in phagocytic or degradative* function of **macrophages**, such that phagosomes become overloaded with undigested bacterial products (histologically foamy macrophages).



Specific type of cystitis with malakoplakia = it is infection "which means inflammation + microorganism" due to intracellular bacteria.

Remember: whenever you have chronic inflammation for long time will stimulate the immune system, and if it is stimulate the immune system long we will have: 1-Autoimmune diseases. 2- Cancer.

[23] Small amount of urine at frequent interval.
[24] Need the toilet NOW.
[25] Painful with urine.
[26] Pus and large number of neutrophils in urine.
[27] Blood in urine, non-specific finding of UTI.
[28] Stones.
[29] devices like Cystoscopy.
[30] Specific type of cystitis.
[31] Strange.

***Michaelis-Gutmann bodies:** A pathognomonic feature of malakoplakia found within the macrophages **+ Foamy cysts.**

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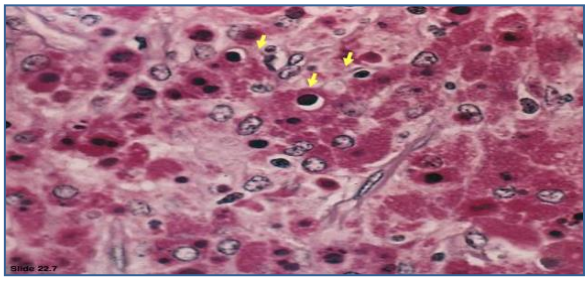
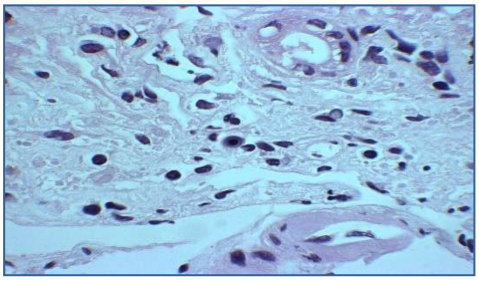
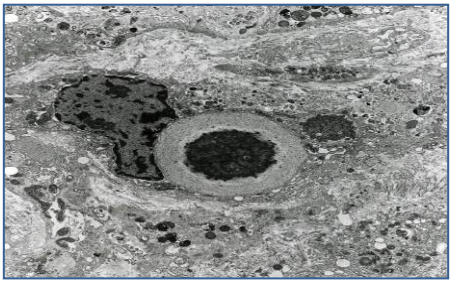
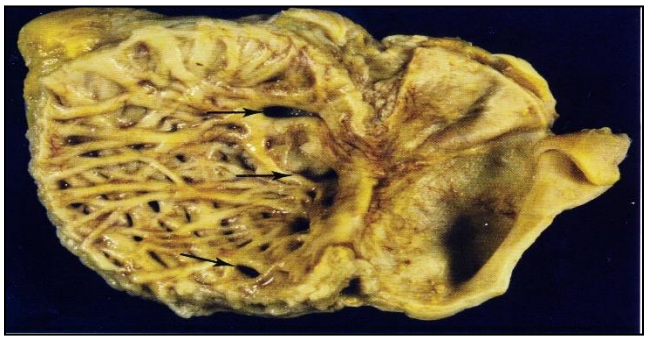
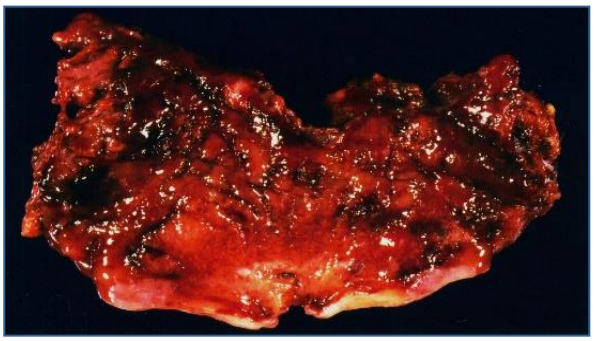








Multiple acquired diverticula (arrows) lie between hypertrophied muscular bundles in a hypertrophied bladder of the patient who had severe prostatic hyperplasia.



Acute inflammation of the urinary bladder.

Hemorrhagic cystitis = inflammation in the bladder itself will be losing blood all the time, they give them Formalin to stop the blood vessels from bleeding. This type is acute.

Radiodensity: (Homework)

Radiopaque calculi[32]	Radiolucent calculi[33]
Referring to a material or tissue that blocks passage of X-rays, and has a bone or near-bone density; radiopaque structures are white or nearly white on conventional X-rays.	(lucere,to shine) pertaining to materials that allow x-rays to penetrate with a minimum of absorption.
Shows: 1- Ca 75-85 % 2- struvite 10-15%	Shows: 1- uric acid 5-8% 2- cystine: 1%

Cystitis:(Keywords)
Frequency, Urgency, Dysuria, Supra-pubic pain, woman, bladder Hematuria, Symptomatic or asymptomatic, foamy macrophages, Michaelis-Gutmann bodies.

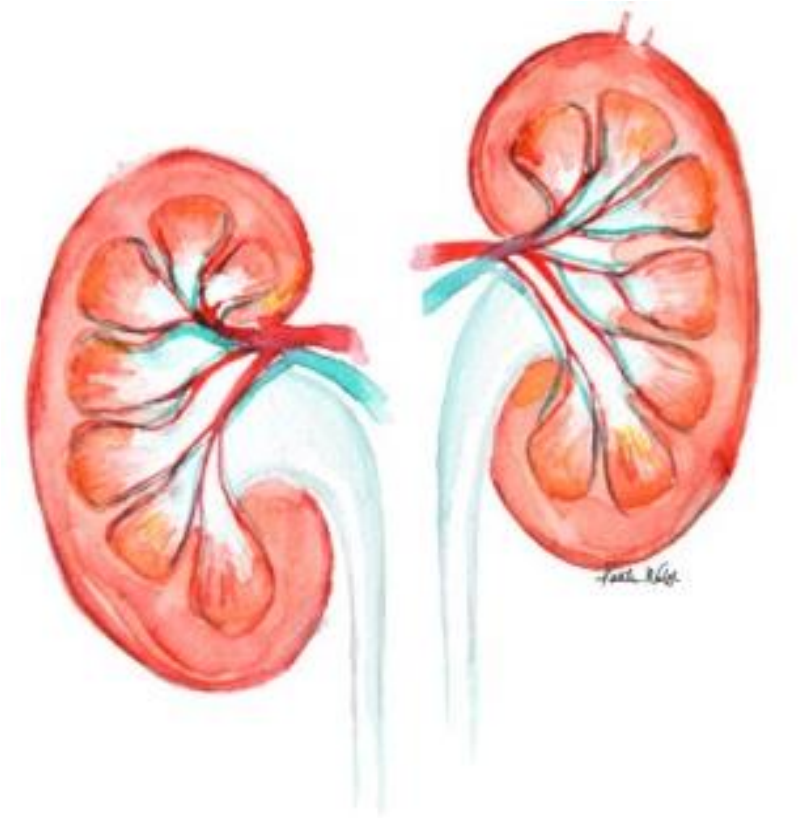
In summary: **Chronic pyelonephritis:**

- TB -> caseating granuloma. - Xanthopylonephritis -> foamy macrophage + granuloma, grossly we'll see staghorn. - Thyrodiazation of the kidney -> dilated tubules and atrophied, and they're filled with PAS positive casts.

- Meanwhile In tubulointerstitial nephritis -> granuloma and eosinophils and it can be acute or chronic.

[32] هي عبارة عن مواد يظهر لونها أبيض تحت الاكس راي زي مثلا حصوات الكالسيوم
[33] هي مواد تظهر شفافة او حتى ما تظهر تحت الاكس راي، لذلك نستخدم ألتراساوند عشان نشوفها زي مثلا حصوات اليوريك أسيد

"اللهم لا سهل إلا ما جعلته سهلًا و أنت تجعل الحزن إذا شئت سهلًا"



Editing File

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القادة

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سمية الغامدي

لمى الفوزان
رنيم الغامدي
دعاء وليد

Thanks to 435 pathology team ☺