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PYELONEPHRITIS
TUBULAR INTERSTITIAL DISEASE

Acute pyelonephritis: Represent one of diseases which is of infective origin and cause tubulo-interstitial diseases.

It is suppurative inflammation caused by pyogenic bacteria.

Most of it follows infection of lower urinary tract, mainly caused by E. coli in 90% followed by decreasing frequency by enterobacter, Klebsiella, Pseudomonas and Proteus.

Bacteria gain access to the urinary tract and kidney by ascending infection and haematogenous.

a. Ascending infection

1. It represents the most common route and the common Pathogenic organism are inhabitant of the colon due to faecal contamination of urethral orifice especially in female during reproductive age. It is attributed to short urethra.

2. Hormonal influence facilitate bacterial adherence to the mucosa.

3. Absence of prostatic secretions which have antibacterial proportions.

4. Urethral trauma during sexual intercourse – the later → honeymoon pyelitis
• Ascending infection also increase in patients with D. M., pregnancy, urinary tract obstruction or instrumentation.

• Bacteria can multiply in urinary bladder where asymptomatic bacteruria found in many case. However, later they can cause cystitis and uretheritis ascending up into the ureter, to renal pelvis and parenchyma. They flow against the flow of urine.

• This mechanism is of importance in chronic pyelonephritis.

• Haematogenous infection less often, it occurs often in patient with obstructive lesion in urinary tract and in debilitated or immunosuppressive patients.
• **Pathology:-** The kidney will be enlarged, swollen with cut surface having yellow-white abscess with large rim. These abscesses will be several millimeter and situated in renal cortex microscopically. There will extensive acute inflammation involving interstitium → obstruction of tubules.

• The glomeruli and Bvs generally show considerable resistance to infection and are spared. The neutrophils will fill-up the tubule and interstitium → neutrophil abscess in renal parenchyma.

• Clinically – APN has an acute onset of chills, fever, loin pain, lumber tenderness, dysuria and frequency of micturation. Urine will show bacterruria > 100,000/ml, pus cells and pus cell casts.
• **Complication**: They are more common in patients in DM or with urinary tract obstruction. These include:

• Papillary necrosis. Necrotizing papillitis in addition it is often associated in patient with analageric nephropathy or sickle cell disease.

• It can affect one or both kidney. The kidney grossly will show necrotic papillae having yellow to gray white, sharply defined area with congested border. Renal pelvis will be dilated. Necrotic area will be separated from viable area by dense zone of polymorphs where the necrotic area will show coagulative necrosis as seen in renal infarction.

• **Pyonephrosis**: This occurs rarely when abscess are extensive particularly in associated with obstruction which cause inability of the abscess to drain which transform the kidney into multiloculated sac filled with pus – this is called pyonephrosis or renal carbuncle.

• Perinephric abscess: This occurs when renal abscess extend through the capsule into the perinephric tissue → perinephric abscess.

• **Chronic pyelonephritis:**

• It is chronic tubulo-interstitial disease resulting from repeated attacks of inflammation and scarring.
Etiopathogenicies:

a. **Reflux nephropathy:**
   - Reflux from the urinary bladder in one or both ureter during micturation represent a major cause of CPN.
   - Vesicoureteric reflux is common in children especially in girls due to congenital absence or shortening of the intravesical portion of the ureter resulting in loss of compression of ureter during act of micturation. This reflux result in increase in presence in the renal pelvis so that the urine is forced in renal tubule → renal damage and scarring. Vesicoureteric reflux is more common in patients with urinary tract infection whether it symptomatic or asymptomatic i.e. even sterile urine can cause damage.
b. Obstructive pyelonephritis:
Obstruction of urine outflow at any level predispose to infection.
Repeated episode of such obstruction and infection → renal damage and scarring.
Rarely recurrent attack of acute pyelonephritis may cause renal damage and scarring.
Grossly the kidney in CPN will be small contracted weighing less than 100 grams. The surface is irregularly scarred and capsule will be stripped off with difficulty due to adherence of scar.
The scar is of variable size and show characteristic U-shaped depression on cortical surface. There is generally dilatation of pelvis and blunted calyces.
Microscopically: The predominant change will be seen in tubule and interstitium.

Interstitium:- Chronic inflammatory reaction mainly made up of lymphocytes, plasma cells and macrophages with fibrosis. Xanthogranulomatous pyelonephritis is uncommon variant characterized by foamy macrophages admixed with other inflammatory cells and giant cells.

Tubules:- Tubules will show atrophy and dilatation where dilated tubule will show eosinophilic colloid casts → thyroidization of tubules.

Pelvicalyceal system:- Renal pelvis and calyces will be dilated and their wall show marked chronic inflammatory cells fibrosis, lymphoid follicles with germinal center can be seen.

BVS:- They will show obliterative endarteritis and changes of hypertensive hyaline arteriosclerosis.

Glomeruli:- The glomerular tuft are intact but there will be periglomerular fibrosis and advanced cases will show hyalinization of glomeruli.
• Clinically they here insidious onset and patient present with picture of chronic renal facture with symptoms of hypertension.

• Sometimes patient present with feature of acute recurrent pyelonephritis i.e. fever, loin pain, lumber tenderness, dysuria, pyouria, bacteriuria and frequency of micturation.
• **Tuberculous pyelonephritis:**
  - Occur due to haematogenous spread from another site, most often from the lung, and less commonly from the ascending infection from tuberculosis of genitourinary symptom as epididymis or fallopian tube. It presents with pyelonephritis or appear as miliary tubercle.
  - Grossly it is often bilateral, involving the medulla with replacement of the papillae by caseous tissue which can accumulate in renal pelvis and calyces causing obstruction.
  - Microscopically it will show typical caseous or non-caseous granuloma. Most patients are middle aged with variable clinical presentation. However, it should be considered in patient with sterile pyouria, microscopic haematuria and mild proteinuria after effective antibiotic therapy for U.T.I.
• **Myelonephropathy** is considered in 50% of patients with multiple myeloma. Its pathogenesis is related to excess filtration of Bence Jone protein usually Kappa light chain.

• These light protein are precipitated in distal convoluted tubules in combination with Tamm-Horsfall proteins (Urinary glycoprotein) → tubular casts which represent laminated eosinophilic particle. These induce peritubular interstitial inflammation.

• The kidney may be normal, or small and shrunken microscopically, there will be tubular atrophy in some while many other will show dilated lumen filled with laminated casts which is surrounded by peritubular interstitial inflammatory reaction with multinucleate giant cells.
• **Nephrocalcinosis:**- This occurs due to diffuse deposits of calcium salts as in hypercalcaemia, hyperphosphateuria and renal tubular acidosis.

• Most commonly occurs as complication of hyperparathyroidism, hyper-vitminnosis D, excessive bone destruction in metastatic malignancy, hyperthyroidism, excessive calcium intake as in milk alkali syndrome, and sarcoidosis.

• Patients will have renal colic, band keratopathy due to calcium deposit in the cornea, visceral metastatic calcification and polyuria, and renal failure.

• Patients with nephrocalcinosis due to hypercalcaemia will show deposition of calcium in tubular epithelial cells in basement membrane, within the mitochondria and the cytoplasm. These concretion → secondary tubular atrophy, interstitial fibrosis and non-specific chronic inflammation in the interstitium.
The markedly enlarged prostate seen here has not only large lateral lobes, but a very large median lobe as well that obstructs the prostatic urethra and led to chronic urinary tract obstruction. As a result, the bladder became both enlarged and hypertrophied as it had to work against the obstruction with every episode of urination. That is why the surface of the bladder appears trabeculated. Note also that a yellowish-brown calculus formed in the bladder.
The small bumps seen here over the ureteral mucosa are called ureteritis cystica and represent cystic areas of glandular metaplasia resulting from inflammation. They are more commonly seen in the bladder, where they are called cystitis cystica.
In the lower pole of this kidney is a 1 cm pale yellow abscess. Infections can reach the kidney either by ascending up the urinary tract (from a bladder infection, for example) or by hematogenous spread with sepsis. This lone abscess was probably hematogenous in origin.
The surfaces of both kidneys demonstrate multiple microabscesses from hematogenous spread of a bacterial infection. The microabscesses have yellow centers and prominent hyperemic borders.
The cut surface of the kidney reveals many small yellowish microabscesses in both cortex and medulla. This type of pyelonephritis is most typical for hematogenous dissemination of infection to the kidney, rather than the more typical ascending urinary tract infection.
This is an ascending bacterial infection leading to acute pyelonephritis. Numerous PMN's are seen filling renal tubules across the center and right of this picture.
At high magnification, many neutrophils are seen in the tubules and interstitium in a case of acute pyelonephritis. The neutrophils can collect in the distal tubules and be passed in urine as WBC casts.
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. [Image courtesy of Dr. John Nicholls, Hong Kong University]
This PAS stain of a renal papilla with a portion of transitional lining epithelium at the lower right demonstrates many budding cells and pseudohyphae of *Candida albicans*. Fungal urinary tract infections are much less common than bacterial infections, but both are likely to be ascending infections, having originated in the lower urinary tract, typically bladder.
The large collection of **chronic inflammatory cells** here is in a patient with a history of multiple recurrent urinary tract infections. This is chronic pyelonephritis.
Both lymphocytes and plasma cells are seen in this case of chronic pyelonephritis. It is not uncommon to see lymphocytes accompany just about any chronic renal disease: glomerulonephritis, nephrosclerosis, pyelonephritis. However, the plasma cells are most characteristic for chronic pyelonephritis.
Sometimes long-standing renal infection may be localized and form a mass-like lesion. This is a disease known as xanthogranulomatous pyelonephritis. It is uncommon, but may mimic a neoplasm.
The microscopic appearance of xanthogranulomatous pyelonephritis shows many pale to foamy macrophages from breakdown of renal parenchyma with ongoing inflammation.
These diagrams illustrate acute tubular necrosis. The distribution of the areas of necrosis is more segmental with ischemic injuries, while toxic injuries result in more diffuse proximal tubular injury.
The epithelium of the tubules seen here is ragged from undergoing necrosis with acute tubular necrosis (ATN) from ischemia. In this case, heart failure with hypotension precipitated the ATN.
The tubular vacuolization and tubular dilation here is a result of the toxic effect of ethylene glycol poisoning. This is representative of acute tubular necrosis (ATN), which has many causes. ATN resulting from toxins usually has diffuse tubular involvement, whereas ATN resulting from ischemia (as in profound hypotension from cardiac failure) has patchy tubular involvement.
In this case of drug-induced interstitial nephritis, there are some scattered eosinophils, along with neutrophils and mononuclear cells in the inflamed interstitium. The classic example of this occurs occasionally with methicillin, but can occur with a variety of drugs such as thiazide diuretics and the H2 blocker cimetidine. The immune mechanism may be either type I or type IV hypersensitivity.
This is chronic urate nephropathy with pale yellowish tan tophaceous deposits in the medulla. There is also an acute urate nephropathy that can occur with a "lysis" syndrome resulting from massive cellular necrosis of leukemia or lymphoma cells with chemotherapy. The metabolic breakdown of the cell nuclei yields large amounts of urate which, when excreted, plug renal tubules.
Chronic urate nephropathy leads to deposition of uric acid crystals in the interstitium, forming tophi with surrounding foreign body inflammation, mononuclear cell infiltrates, and fibrosis. The long, needle-shaped crystals form the pale mass shown here at high magnification. Patients with hyperuricemia may also have nephrolithiasis with uric acid stones.
This is a renal biopsy at low magnification in which there is a **focal lesion** centered around a blood vessel. Thus, a vasculitis is present. The one **glomerulus** at the lower center appears normal. An adequate renal biopsy should contain at least 6 glomeruli so that there is less chance that focal lesions will be missed. Renal biopsies are often performed with ultrasound guidance.
At high power, the vasculitis is seen to involve a renal artery branch. This is a necrotizing granulomatous vasculitis. In this case, the anti-neutrophil cytoplasmic autoantibody (ANCA) serology was positive and a diagnosis of Wegener granulomatosis was made. This patient also had pulmonary involvement with this disease.
Here is a vasculitis of a renal arterial branch. Lymphocytes are scattered in and around the vessel. This happens to be the classic form of polyarteritis nodosa (PAN), a systemic vasculitis that most often affects the kidneys. The ANCA serology is often negative.
A small platelet-fibrin thrombus is seen in a glomerular capillary above the arrow. This occurred in a patient with thrombotic thrombocytopenic purpura (TTP). This rare coagulopathy mainly affects kidneys, heart, and brain with small arteriolar thrombi. Acute renal failure can occur. The classic pentad of fever, acute renal failure, neurologic changes, thrombocytopenia, and microangiopathic hemolytic anemia is often present. TTP results from a congenital or more often acquired defect in the ADAMTS-13 metalloproteinase enzyme that cleaves vonWillebrand factor (vWF) multimers, and the large multimers lead to abnormal platelet aggregation. TTP overlaps with hemolytic uremic syndrome (HUS) that may be precipitated by verotoxins from such organisms as *E. coli* (type O157:H7) that cause endothelial injury.
Very similar to thrombotic thrombocytopenic purpura (TTP) is hemolytic-uremic syndrome (HUS). The two conditions may be difficult to tell apart. HUS can be a leading cause for acute renal failure in children. Ingestion of foods, such as poorly cooked ground beef, introduces a verotoxin-producing *E. coli* infection into the GI tract. Such strains are often identified by serotyping, typically type O157:H7. A bloody diarrhea is followed in a few days by renal failure caused by endothelial injury from the toxin, leading to the characteristic fibrin thrombi in glomerular and interstitial capillaries. Most patients recover in a few weeks with supportive dialysis.
Here is an example of renal vascular disease known as benign nephrosclerosis. The smaller arteries in the kidney have become thickened and narrowed. Hyaline arteriolosclerosis with hypertension or diabetes mellitus is usually present. This leads to patchy ischemic atrophy with focal loss of parenchyma that gives the surface of the kidney the characteristic granular appearance as seen here.
In malignant nephrosclerosis, the kidney demonstrates focal small hemorrhages. This is often due to an accelerated phase of essential hypertension in which blood pressures are very high (such as 300/150 mm Hg).
Malignant hypertension leads to fibrinoid necrosis of small renal arteries as shown here. The damage to the arteries leads to formation of pink fibrin--hence the term "fibrinoid".
Thickening of the arterial wall with malignant hypertension also is associated with a hyperplastic arteriolosclerosis (hyperplastic arteriolitis). This arteriole has an "onion skin" appearance.
This is nodular glomerulosclerosis (the Kimmelstiel-Wilson lesion) of diabetes mellitus. Nodules of pink hyaline material form in regions of glomerular capillary loops in the glomerulus. This is due to a marked increase in mesangial matrix from damage as a result of non-enzymatic glycosylation of proteins.
This is a PAS stain of nodular glomerulosclerosis (Kimmelstiel-Wilson disease) in a patient with long-standing diabetes mellitus. Note also the markedly thickened arteriole at the lower right which is typical for the hyaline arteriolosclerosis that is seen in diabetic kidneys as well.
This PAS stain demonstrates diffuse glomerulosclerosis associated with long-standing diabetes mellitus. There is an increase in mesangial matrix, a slight increase in mesangial cellularity, and capillary basement membrane thickening. These changes gradually advance until the entire glomerulus is sclerotic.
The end result of many renal diseases -- whether they are renal vascular diseases, glomerulonephritis, or chronic pyelonephritis--is end stage renal disease (ESRD). In ESRD, the kidneys are small bilaterally, as shown here. This condition is associated with chronic renal failure, and the patient's blood urea nitrogen (BUN) and serum creatinine continue to increase. Chronic renal failure can be treated by dialysis or by kidney transplantation, as shown here.
The microscopic appearance of the "end stage kidney" is similar regardless of cause, which is why a biopsy in a patient with chronic renal failure yields little useful information. The cortex is fibrotic, the glomeruli are sclerotic, there are scattered chronic inflammatory cell infiltrates, and the arteries are thickened. Tubules are often dilated and filled with pink casts and give an appearance of "thyroidization."
In this case, severe atherosclerosis in a patient with diabetes mellitus led to severe aortic atherosclerosis with renal arterial stenosis as well as nephrosclerosis and nodular glomerulosclerosis of the kidneys. The end stage renal disease was treated with renal transplantation. The transplant kidney is placed in the pelvis because this is technically easier and there is usually no point in trying to remove the native kidneys. In this case, the patient developed chronic rejection and that is why focal hemorrhages are seen in the kidney that is slightly swollen. A radiographic study would show decreased renal blood flow in the transplant kidney.
This kidney was removed because of acute transplant rejection. Note the swollen and hemorrhagic appearance of this entire kidney.
Seen here is acute tubulointerstitial cellular rejection of a renal transplant. This can occur days to months to years following transplantation. Both CD4 and CD8 lymphocytes participate in this rejection reaction. The immunosuppressive drugs such as cyclosporine given to counteract the rejection may lead to nephrotoxicity with similar changes as well.
This is chronic vascular rejection of a renal transplant, which has a poor prognosis. Note the thickened arteries with intimal fibrosis and chronic inflammation. These changes gradually occur over months in affected patients.