Calcification

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Questions

- Dystrophic and metastatic calcification. Organ manifestations
- Pathomechanism and clinicopathology of calcification

Definition of calcification
Two types

Pathologic calcification is the abnormal deposition of calcium salts.

When the deposition occurs in dead or dying tissues, it is called dystrophic calcification.

It occurs in with normal serum levels of calcium. Calcium metabolism is normal.

In contrast, the deposition of calcium salts in normal tissues is known as metastatic calcification and is almost always secondary to some derangement in calcium metabolism - hypercalcemia.

Of note, while hypercalcemia is not a prerequisite for dystrophic calcification, it can exacerbate it.

Dystrophic calcification

- Dystrophic calcification is encountered in areas of necrosis of any type.
- It is virtually inevitable in the atheromas of advanced atherosclerosis.
- Calcification can develop in aging or damaged heart valves, resulting in severely compromised valve motion. Dystrophic calcification of the aortic valves is an important cause of aortic stenosis in elderly persons.

Dystrophic calcification

The pathogenesis of dystrophic calcification involves initiation (or nucleation) and propagation, it may be intracellular or extracellular; the end product is the formation of crystalline calcium phosphate.

Initiation in extracellular sites occurs in matrix vesicles, and in pathologic calcification they derive from degenerating cells.

Initiation of intracellular calcification occurs **in the mitochondria** of dead or dying cells that have lost their ability to regulate intracellular calcium.

After initiation in either location, propagation of crystal formation occurs.

Psammoma bodies

- Psammoma bodies are concentric lamellated calcified structures, observed most commonly meningioma.
- They represent a process of dystrophic calcification.

Importance of calcification

Metastatic calcification

Metastatic calcification can occur in normal tissues whenever there is hypercalcemia.

The major causes of hypercalcemia are

1. increased secretion of parathyroid hormone,due primary parathyroid tumors
2. destruction of bone due to the effects of accelerated turnover, immobilization, or tumors
3. vitamin D–related disorders
4. renal failure, in which phosphate retention leads to secondary hyperparathyroidism.

Morphology of calcification

- Regardless of the site, calcium salts are seen on gross examination as fine white granules or clumps.
- Dystrophic calcification is common in areas of caseous necrosis in tuberculosis.
- On histologic examination, calcification appears as intracellular and/or extracellular basophilic deposits.
- Over time, heterotopic bone may be formed in the focus of calcification.

Metastatic calcification can occur widely throughout the body but principally affects the vasculature, kidneys, lungs, and gastric mucosa.
It may produce respiratory deficits, and massive deposits in the kidney **(nephrocalcinosis)** can lead to renal damage.

Stone formation

- Pathomechanism and clinicopathology of calcification
- Cholelithiasis and urolithiasis

Cholelithiasis (Gallstones)

Stone formation anywhere in the biliary tree.

Gallstones afflict 20% of adults residing in Western countries, 40% in Latin American countries, and 4% in Asian countries.

In the United States, about 1 million new cases of gallstones are diagnosed annually, and two thirds of these patients undergo surgery.

There are two main types of gallstones: cholesterol stones, containing crystalline cholesterol (80% of stones in the West), and pigment stones, made of bilirubin calcium salts.

Etiology of gallstones

Age and gender. The prevalence of gallstones increases throughout life. The prevalence in women is twice as high as in men.
Ethnic and geographic. Cholesterol gallstone prevalence approaches 75% in certain Native American populations (cholesterol hypersecretion).
Environment. Estrogenic influences, including oral contraceptives, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol. Obesity, rapid weight loss also are associated with increased biliary cholesterol secretion.
Acquired disorders. Any condition in which gallbladder motility is reduced predisposes to gallstones, such as pregnancy, rapid weight loss.

Mechanism of stone formation

Bile formation is the only significant pathway for elimination of excess cholesterol from the body.

Cholesterol is rendered water-soluble by aggregation with bile salt.

When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol crystallizes out of solution.

Cholesterol gallstone formation is enhanced by **hypomobility of the gallbladder** (stasis), which promotes nucleation, and by **mucus hypersecretion,** with consequent trapping of the crystals, thereby enhancing their aggregation into stones.

Formation of pigment stones is more likely in the presence of unconjugated bilirubin in the biliary tree, as occurs in hemolytic anemias. The precipitates are primarily insoluble calcium bilirubinate salts.

Cholesterol stones

- arise exclusively in the gallbladder
- consist of 50% to 100% cholesterol
- pure cholesterol stones are pale yellow
- they are ovoid and firm
- they can occur singly, but most often there are several
- They have faceted surfaces resulting from their apposition
- most cholesterol stones are radiolucent (black on X-ray, you cannot see them)

Pigment stones

- may arise anywhere in the biliary tree and
- are classified into black and brown stones.
- In general, black pigment stones are found in sterile gallbladder bile, while brown stones are found in infected intrahepatic or extrahepatic ducts.
- The stones contain calcium salts of unconjugated bilirubin and other calcium salts and mucin.
- Black stones are usually small, fragile and numerous.
- Brown stones tend to be single or few in number and to have a soft, greasy, soaplike consistency.
- Because of calcium carbonates and phosphates, black stones are radiopaque (visible on X-ray).

Clinical features

- 80% of individuals with gallstones remain asymptomatic throughout life.
- In the unfortunate minority symptoms are striking. There is usually pain, which typically localizes to the right upper quadrant.
- Such “biliary” pain is caused by gallbladder or biliary tree obstruction, or by inflammation of the gallbladder itself.
- More severe complications include **empyema**, **perforation**, **fistulas**, **inflammation** of the biliary tree and **pancreatitis**.
- The larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction.
- It is the very small stones, or “gravel,” that are more dangerous.
- Occasionally a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction (*gallstone ileus*).

ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) is a combination of two procedures: an endoscopy and an X-ray.
An endoscopy is a procedure in which a thin, flexible tube attached to a tiny camera is threaded down to the gastrointestinal tract. This camera will be used to take an X-ray of the insides of the bile ducts and pancreatic ducts.

Urolithiasis (kidney stones)

- Urolithiasis is calculus formation at any level in the urinary collecting system, but most often the calculi arise in the kidney.
- By the age of 70 years, 10% of men and 5% of women in the US will have experienced a symptomatic kidney stone.
- Symptomatic urolithiasis is more common in men than in women.
- A familial tendency toward stone formation has long been recognized.

Pathogenesis – calcium stone

The **most important** cause of stone formation **is increased urinary concentration of the stone's constituents, so that it exceeds their solubility in urine (supersaturation).**

Predisposing: the concentration of the urine, changes in urine pH, and bacterial infections.

Hypercalcemia can cause stones and nephrocalcinosis as well.

As shown in, 50% of patients who develop **calcium stones** have hypercalciuria that is not associated with hypercalcemia. Most in this group absorb calcium from the gut in excessive amounts **(absorptive hypercalciuria)** and promptly excrete it in the urine, and some have a primary renal defect of calcium reabsorption **(renal hypercalciuria).**

Pathogenesis of different stone types

- **Calcium stones**: about 80% of renal stones are composed of either calcium oxalate or calcium oxalate mixed with calcium phosphate.
- **Magnesium ammonium phosphate (struvite) stones:** almost always occur in persons with a persistently alkaline (high pH) urine resulting from UTIs.
- **Uric acid stones**: gout and diseases involving rapid cell turnover (malignancies) lead to high uric acid levels in the urine and the possibility of uric acid stones. About half of people with uric acid stones, however, have neither hyperuricemia nor increased urine urate but demonstrate an unexplained tendency to excrete a persistently acid urine (low pH).
- **Cystine stones** are associated with a genetic defect in the renal transport of cystine. Like uric acid stones, cystine stones are formed when the urine is acidic.

Morphology

- Stones are usually unilateral.
- Common sites of formation are the renal pelvis and calyces and the bladder.
- Often, many stones are found in one kidney. They tend to be small (feww mms) and may be smooth or jagged.
- Occasionally branching structures known as **staghorn calculi** are present, which create a cast of the renal pelvis.

Clinical features

- Stones may be present without producing either symptoms or renal damage.
- This is particularly true with large stones lodged in the renal pelvis.
- Smaller stones may pass into the ureter, where they may lodge, producing a typical intense pain known as renal or ureteral colic, characterized by paroxysms of strong pain radiating toward the groin. Often there is gross hematuria.
- The clinical significance of stones lies in their capacity to obstruct urine flow or to produce sufficient trauma to cause ulceration and bleeding.
- They also predispose to bacterial infection.
- Fortunately, in most cases the diagnosis is readily made radiologically.

Kidney stone removal

- Ultrasound waves
- Ureteroscopy: crush or basket out
- Percutaneous lithotomy