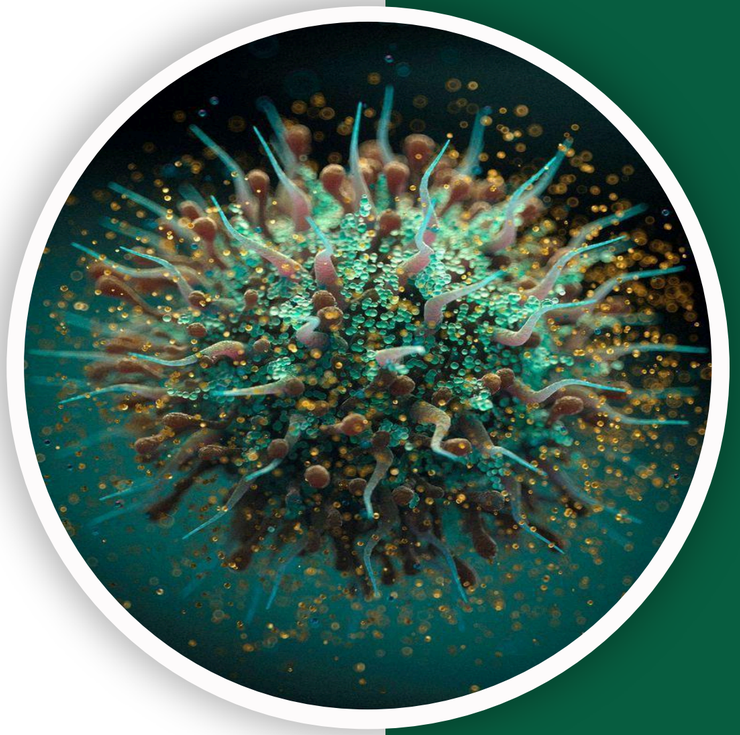
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | FINAL 5

α1-Antitrypsin, Reys Budd Chiari, Biliary Peliosis Hepatis



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Important

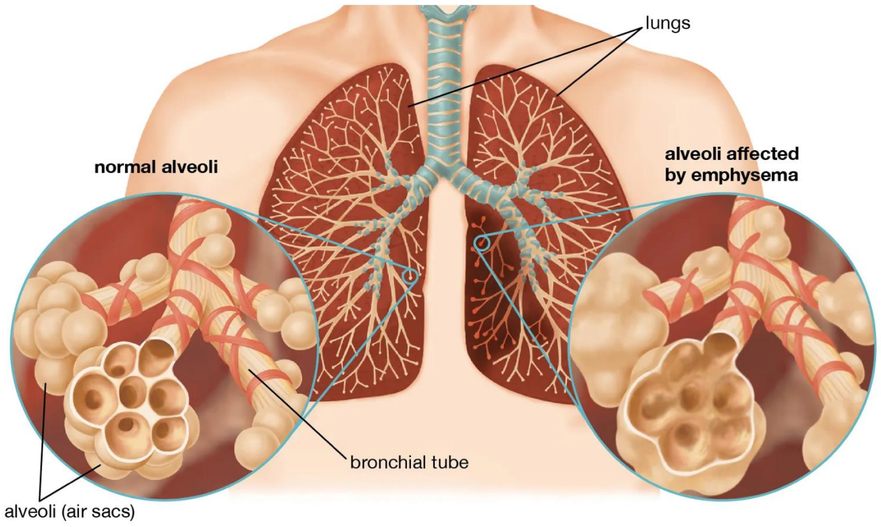
This modified is special because the doctor was only reading from the slides during the lecture, so we used multiple resources while preparing it to make studying easier for you.

NST

α-1-Antitrypsin Deficiency

- ❑ What is **trypsin** ?
- ✓ It is **one of the proteases** that are **released during inflammatory response** to degrade proteins and allow WBC to reach the site of inflammation.

- ❑ What is **α-1-Antitrypsin** ?
- ✓ **α-1-Antitrypsin :** it is an plasma glycoprotein that **inhabit proteases** particularly neutrophil elastase, cathepsin G, and proteinase 3,which are **released from neutrophils** at sites of inflammation. **α-1AT deficiency** leads to unopposed activation of neutrophil proteases (e.g., elastase), which **destroy elastic fibers in alveolar walls**, resulting in **pulmonary emphysema.**



Extra image

α-1-Antitrypsin Deficiency

- **Autosomal Recessive disorder.**
- **freq. 1:7000 in N. American white population**
- **α-1-antiryrpsin is a protease inhibitor as elastase, cathepsin G , proteinase 3 which are released from neutrophils at the site of inflammation**
- **The gene pi. Is located on chr.14 (Pi = Protease inhabitor).**

α-1-Antitrypsin Deficiency

- **At least 75 forms of gene mutation are present.**
- The three most clinically important forms of Pi gene are :

  1. **PiMM** : Wild-type gene.
  2. **PiMZ** : Contains **one mutant allele** and **one wild-type allele**.
  3. **PiZZ** : **Both alleles are mutated** and people who have this gene are at higher rate of developing clinical disease.

- **The most common genotype is pi.MM present in 90% of individuals.**
- **PiZZ genotype → ↓ level of α-1-antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease.**
- PiMZ heterozygotes have intermediate plasma levels of α-1AT.

Pathogenesis

- **The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes.**

- **Although all individual with PiZZ genotype accumulate α-1-AT-Z protein, only 10% of them develop clinical liver disease. This is due to lages (differences between people) in ER protein degradation pathway.**

Pathogenesis

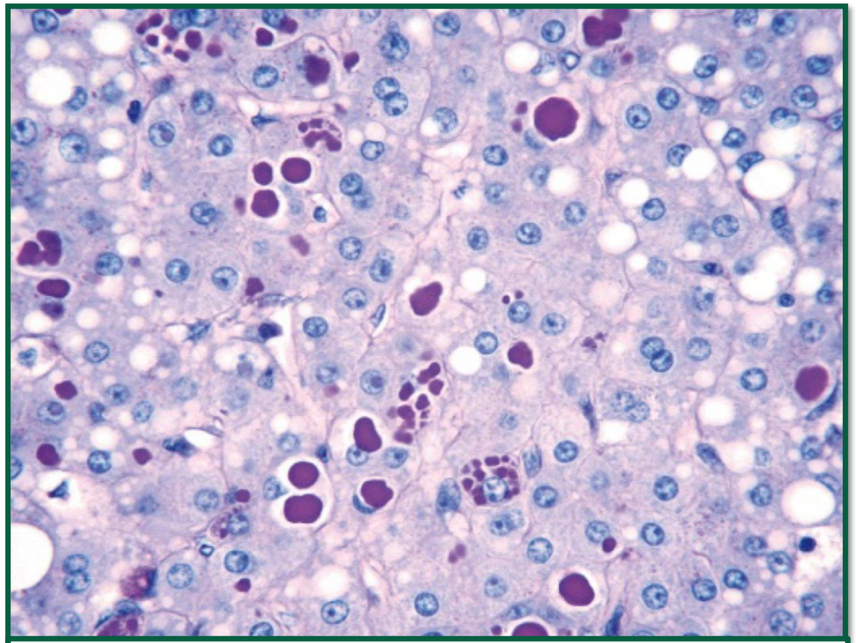
- **The accumulated α-1-AT-Z is not toxic but the autophagocytic response stimulated within the hepatocytes appear to be the cause of liver injury by autophagocytosis of the mitochondria.**

- **8-10% of patients develop significant liver damage.**

Morphology

- Intracytoplasmic globular inclusions in hepatocytes.
  - which are acidophilic in H&E. sections under light microscope.

- The inclusions are PAS +ve & diastase resistant.
- Neonatal hepatitis cholestasis & fibrosis.
- Chronic hepatitis.
- Cirrhosis.
- Fatty change.
- Mallory bodies.



Extra image: a1-Antitrypsin de ciency. Periodic acid-Schiff (PAS) stainafter diastase digestion of the liver highlights the characteristic magentacytoplasmic globules.

Clinical features

- **Neonatal hepatitis with cholestatic jaundice appears in 10–20% of newborns with the disease.**

- **Attacks of hepatitis in adolescance** may subside with apparent complete recovery, or they may become :
- **Chronic hepatitis & cirrhosis. chronic and lead progressively to cirrhosis.** Alternatively, the disease may remain silent until cirrhosis appears in middle to later adult life.

- **HCC in 2 — 3 % of PiZZ adults ± cirrhosis** (Usually in setting of cirrhosis).

Reye Syndrome

- The presentation usually comes in ***child who take aspirin (salicylate) while having a viral infection or recently recovering from one.***

- The aspirin normally work as a decoupler of the mitochondrial electron transport chain & oxidative phosphorylation, but it's effect is mild to cause liver damage. However, using aspirin along with viral infection aggravates this effect.

- **Fatty change in liver & encephalopathy.**

- **< 4 yr. (child)**

- **5 – 3d after viral illness. (Recovering)**

- **↑ liver & abn. LFT Vomiting lethargy. 25% may go into coma.**

Pathogenesis

- **Derangement of mitochondrial function along or in combination with viral infection & salicylate.**
- **Microvesicular steatosis.**
- **Brain edema.**
- **Absent inflammation.**
- **Sk. Muscles, heart, kidneys – fatty change.**

Reye Syndrome pathoma
High-Yield Notes

- **REYE SYNDROMEA.**

1. Fulminant liver failure and encephalopathy in children with viral illness who take aspirin.

2. Likely related to mitochondrial damage of hepatocytes.

3. Presents with hypoglycemia, elevated liver enzymes, and nausea with vomiting; may progress to coma and death.

Budd – Chiari Syndrome

- **Thrombotic occlusion of the hepatic vein.**

- **Hepatomegaly**
- **Wt.gain**
- **Ascitis liver,** congestion causes decreased liver function → decreased level of albumin.
- **Abd. Pain** (RUQ pain).

Budd – Chiari Syndrome causes

1) **PCV (Polycythemia vera)**
   - Increased RBC mass → blood becomes more viscous → thrombosis tendency increases → hepatic vein thrombosis can occur.

2) **Pregnancy.**
   - Pregnancy is a physiologic hypercoagulable state:
     1) Increased clotting factors
     2) Reduced fibrinolysis
     3) Venous stasis from enlarged uterus → predisposes to hepatic vein thrombosis.

3) **Postpartum.**
4) **Oral contraceptive.**

Budd – Chiari Syndrome causes

5) PNH (Paroxysmal nocturnal hemoglobin)

- Causes abnormal complement mediated hemolysis and a marked tendency for thrombosis, especially in unusual veins such as hepatic veins.

6) Mechanical Obstruction.

7) Tumors as HCC.

8) Idiopathic in 30% of the cases.

Morphology

- The hepatic vein occlusion will result in **retention of blood in the liver and portal vein** which results in **hepatomegly (liver enlargement) & liver congestion (since it is full of blood)** and **portal hypertension**.

- The hepatomegly will result in compression over the hepatic artery which **causes ischemia to the liver especially the peri-central part (most distance from portal tract) which result in necrosis.**

- **Swollen liver, red with tense capsule.**
- **Ventrilobular congestion & necrosis.**
- **Fibrosis.**
- **Thrombi**

- **Clinically**
  - **Mortality rate is high if not treated.**

Primary sclerosing cholangitis

- Many features of PSC suggest immunologically mediated injury of bile ducts (it can be caused by other causes such as toxins or ischemia to biliary tree, etc.).

- **Inflammation, obliterative firosis, & segmental dilation of the obstructed.**
- **Intra hepatic & extra hepatic bile ducts.**
- **In PSC, UC coexists in 70% of patients.**
- **In patients of UC, 4% develop PSC.**
- **3-5 the decades.**
- **M: F 2:1.**

Primary sclerosing cholangitis

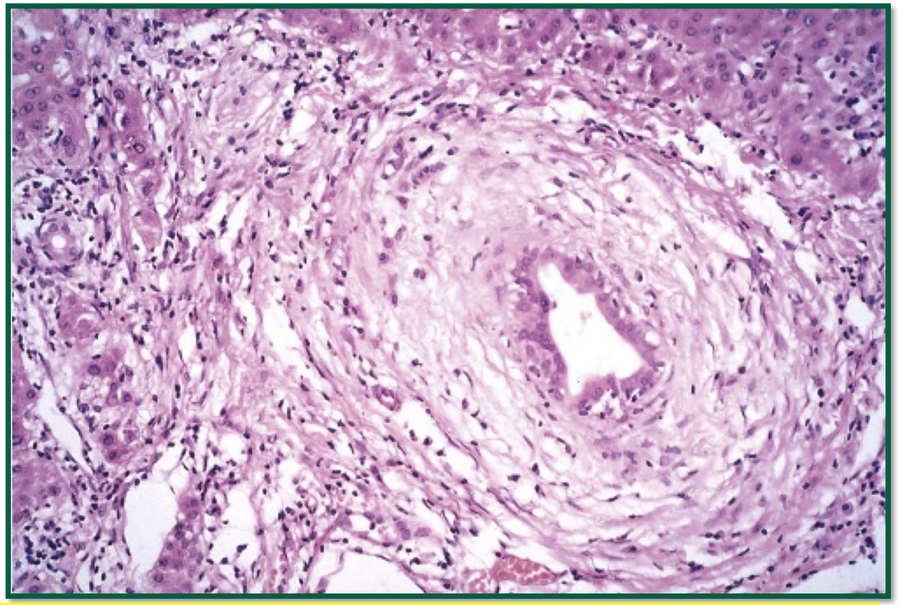
- Asymptomatic pts.
- Persistent ↑serum alkaline phosphatase.
- Fatigue, pruritis, jaundice, wt. loss, ascitis, bleeding, encephalopathy

- Antimitochondrial Abs < 10% of cases.
- Antinuclear cytoplasmic Abs in 80% of cases.

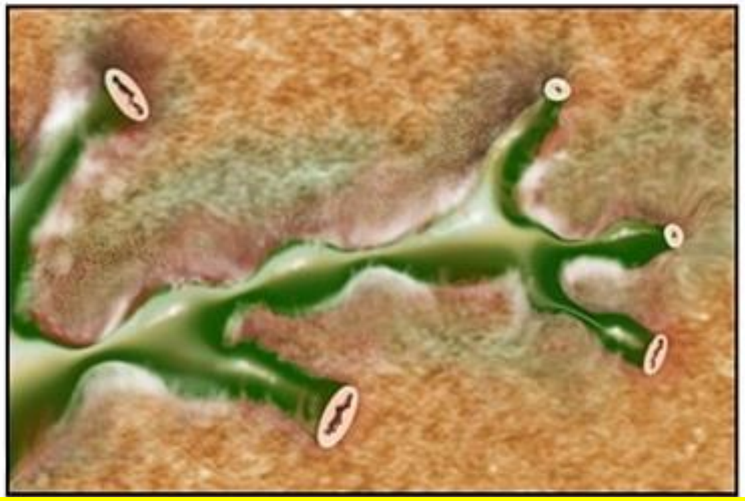
- Very important in distinguishing it from Primary Biliary Cirrhosis In which it has AMA in 90-95% of patients.

Morphology

- Concentric periductal onion-skin fibrosis & lymphocytic infilrate.
- Atrophy & obliteration of bile ducts.
- Dilation of bile ducts inbetween areas of stricture.
- Cholestasis & fibrosis.
- Cirrhosis, cholangiocarcinoma (10 – 15%).



Extra image: “onion-skin” concentric scar



Extra image: constricted stricter between dilated areas of bile ducts

Pathogenesis

- Exposure to gut derived toxins
- Immune attack
- Ischemia of biliary tree

Secondary biliary cirrhosis

- Prolonged obstruction of extrahepatic biliary tree

- **Causes:**
  1) cholelithiasis
  2) biliary atresia **(caused by inflammatory response).**
  3) Malignancies
  4) stricutres

Primary sclerosing cholangitis

Pathoma High-Yield Notes

A. Inflammation and fibrosis of intrahepatic and extrahepatic bile ducts.
   1. Periductal fibrosis with an'onion-skin' appearance.
   2. Uninvolved regions are dilated resulting in a"beaded" appearance on contrastimaging

B. Etiology is unknown, but associated with ulcerative colitis; p-ANCA is often positive.

C. Presents with obstructive jaundice; cirrhosis is a late complication.

D. Increased risk for cholangiocarcinoma.

Primary biliary Cirrhosis

Pathoma High-Yield Notes:

A. Autoimmune granulomatous destruction of intrahepatic bile ducts
   1. Classically arises in women (average age is 40 years)
   2. Associated with other autoimmune diseases

B. Etiology is unknown; antimitochondrial antibody is present.

C. Presents with features of obstructive jaundice

D. Cirrhosis is a late complication.

- **chronic, progressive & often fatal cholestatic liver disease.**

- **Non-suppurative granulomatous destruction of medium-sized intrahepatic bile ducts, portal inflammation & scarring.**

- **Age 20-80yrs (peak 40-50yrs).**
- **F > M**
- **Insidious onset**
- **Pruritis, jaundice**
- **Cirrhosis over 2 or more decdes**

- Most patients are diagnosed in the early stages of disease following a workup triggered by the identification of an elevated serum alkaline phosphatase level or severe itching.
- Hypercholesterolemia is common.
- The disease is confirmed by liver biopsy, which is considered diagnostic **if a florid duct lesion is present**.
- Symptom onset is insidious, with patients typically noticing slowly increasing fatigue and pruritus.

- **↑Alkaline phosphatase & cholesterol.**
- **Hyperbilirubinemia = hepatic decompansation**
- **Antimitochondrial Abs > 90%**
- **Antimitochondrial pyruvate dehydrogenase**
- **Associated conditions: sjogern synd.**
  - **Scleroderma thyroiditis, RA, Raynauds phenomenon. MGN, celiac disease.**

❑ Morphology:

- **interlobular bile ducts are absent or severely destructed (florid duct lesion)**
- **intra epithelial inflammation**
- **Granulomatous inflammation**
- **Bile ductular proliferation**
- **Cholestesis**
- **Necrosis of parenchyma**
- **Cirrhosis**

Sinusoidal Obstruction Syndrome (Veno-occlusive disease)

- Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids.
- This occurs in the first 20-30 days after bone marrow transplantation.
- Which is caused by:
  - Drugs as cyclophosphamide.
  - Total body radiation.

Sinusoidal Obstruction Syndrome (Veno-occlusive disease)

- Occlusive events can occur in any caliber of hepatic vein branches.
- Occlusion of the smallest intrahepatic branches is known as sinusoidal obstruction syndrome (formally known as veno-occlusive disease). A rare but well-known cause of this syndrome is consumption of pyrrolizidine alkaloide containing Jamaican bush tea; more commonly hepatic vein thrombosis occurs following allogeneic hematopoietic stem cell transplantation, usually within the first 3 weeks, or in cancerpatients receiving chemotherapy.

- The obstruction of the major hepatic veins produces liver enlargement, pain, and ascites, a condition known as Budd-Chiari syndrome. Only when two or more major veins are obstructed does intrahepatic blood pressure rise to the point of causing hepatic dam-age. Hepatic vein thrombosis is associated with the same hypercoagulable states as portal vein thrombosis and includes intraabdominal cancers, particularly hepatocellular carcinoma. As is often the case in those affected by various thrombotic disorders, Budd-Chiari syndrome frequently occurs in patients with several risk factors, such as pregnancy or oral contraceptive use combined with an underlying thrombophilic disorder.

Incidence

-20% in recepients of allogeneic marrow transplant

Clinical presentation

Mild – severe

Death if does not resolve in 3 months

-

Mechanism

1) Toxic injury to sinusoidal endothelium → emboli (cellular debris, blood clots, fats).
2) → blockage of bl. Flow
3) Passage of blood into space of Disse (the bile duct space). →↑ stellate cells → fibrosis.

Peliosis Hepatis

- **Sinusoidal dilatation**
- **Causes:**
  1) **anabolic steroids**
  2) **oral contraceptive**
  3) **danazol**

✓ **Pathogenesis Unknown**

Clinical Features

- **Asymptomatic.**
- **Intra abdominal hemorrhage.**
- **Liver failure.**

- **Reversible.**

رسالة من الفريق العلمي (الجزء ١):

نظن أحيانًا أننا قادرون على العيش بمفردنا، قادرون على إكمال الطريق بأنفسنا، لكننا في النهاية بشر ...بشر ضعفاء، خلقنا الله شعوبًا وقبائل لنتعارف، وفضّل بعضنا على بعض في الرزق ليتخذ بعضنا بعضًا سُخريًا؛ فنحن بحاجة إلى بعضنا البعض في هذه الحياة.
وعلى قدر ما يبدو هذا الكلام بديهيًا، فإنه مهمّ الذكر في عصرٍ انتشرت فيه الفردانية، والنظرة المادية للأمور، والنظر إلى الإنسان على أنه رقم، لا على أنه العالم الأكبر الذي انطوى فيه الكون.
وعلى ذكر الأرقام والفردانية، إن كنت ممن غُسلت عقولهم بفكرة أن الرجل يُقاس بما يملك من مال، والمرأة بما تملك من جمال، فإني أدعوك لأن تفكر خارج حدود الصندوق الذي وضعك الإعلام فيه.

هل هذه المقارنات عادلة أصلًا؟
إن مقارنة النساء بالجمال مقارنة ظالمة، لأنك تقارن الإنسان بشيء لم يختره، ثم تحكم عليه بناءً على ذلك، فكأنك حكمت على بريء بالإعدام.
وكذلك مقارنة الرجال بالمال؛ فكم من رجل وُلد غنيًا، وكم من رجل بدأ فقيرًا ثم أصبح غنيًا، وكم منهم بقي فقيرًا.

فهل تصح المقارنة بينهم؟

سأجيب عن هذا السؤال بسؤال:
هل توافرت لهم الظروف النفسية والفيزيائية نفسها؟
كلا، وألف كلا.
فلا يمكن أن تتطابق ظروف شخصين في هذه الحياة، وحتى إن تشابهت الظروف، فإن النيات تختلف، والله وحده علّام الغيوب.

رسالة من الفريق العلمي (الجزء ٢):

ولو نظرنا إلى ميزان التفاضل عند الله، لوجدنا أنه التقوى، قال تعالى:
﴿إِنَّ أَكْرَمَكُمْ عِندَ اللَّهِ أَتْقَاكُمْ﴾.

وقال رسول الله صلى الله عليه وسلم» :إذا جاءكم من ترضون دينه وخلقه فزوّجوه، إلا تفعلوا تكن فتنة في الأرض وفساد كبير .«فلم يقل :من ترضون ماله أو جماله؛ لأن المال دون تقوى لا قيمة له، والجمال لا يدوم، ومن جعل غايته الجمال ملَّ يومًا منه.
ولكن ...من يكون ذلك الشخص الذي تشكو له همّك وحزنك؟
أأخٌ هو أم أخت؟
صديق أم صديقة؟
زوج أم زوجة؟
كم أود أن أقول لك :لا تشكُ همّك إلا لله...
لكن النفس البشرية تميل بطبعها إلى من يؤنسها، إلى إنسان يجلس بجانبها، إلى كتف تبكي عليه.
وليس في الفضفضة نقصٌ في الإيمان، بل هي من الفطرة التي خلقنا الله عليها.
فقد شكا خير البشر، رسول الله محمد صلى الله عليه وسلم، إلى أمنا خديجة رضي الله عنها ما أصابه حين رأى جبريل عليه السلام في غار حراء، فعاد خائفًا مرتجفًا، فكانت له خير الزوجة؛ طمأنته، وهدّأت روعه، ولم تتركه وحيدًا مع خوفه.

وإن لم تكن كتفًا يبكي عليه من تحب، فلا تتوقع أن تجد كتفًا تبكي عليه.
وإن لم تكن سندًا لمن حولك، فلا تتعجب إن سقطت يومًا ولم تجد من يسندك.

رسالة من الفريق العلمي (الجزء ٣):

وتذكّر:

تلك اليد التي أفلتتك مرة ...لا يعني أنها تعمدت ذلك!

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			