JUST ANOTHER LFT ABNORMALITY REFERRAL

2019 Annual Update in Medical Hepatology

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PATIENT K

- 18 year old white male with no significant past medical history presents with LFT abnormalities found prior to Accutane treatment

- Recently, mother has noticed some mild yellow tinge in his eyes and to his skin

- ROS
  - + chronic diarrhea, intermittent headaches
  - - fevers, chills, abdominal pain, nausea, vomiting, pruritus, changes in appetite, weight loss

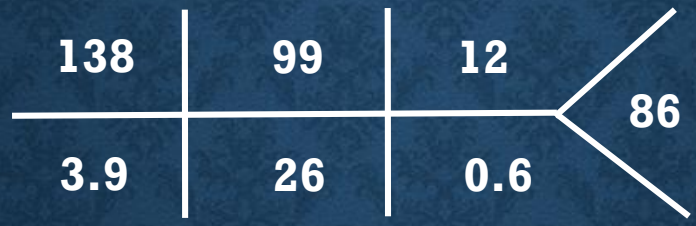
MEDICAL HISTORY

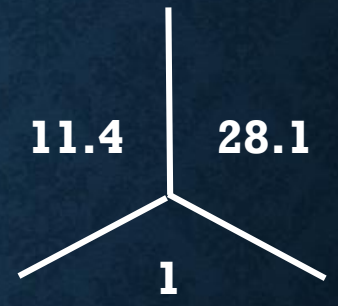
- Past Medical History
  - Acne vulgaris
  - Recurrent strep throat
- Past Surgical History
  - Tonsillectomy
- Family History
  - Brother – insulin-dependent diabetes mellitus, hypercholesterolemia
  - Maternal grandparents – hypercholesterolemia
- Social History
  - In high school
  - Does not smoke, drink or use any illicit drugs
  - No tattoos, piercing, foreign travels
- Allergies
  - Dog dander
- Medications
  - Previously on minocycline for acne
  - No OTC including herbal supplements

PHYSICAL EXAMINATIONS

- Vital Sign: T 37.5 °C, BP 110/72, HR 80, RR 14, SatO2 98%, BMI 22.3, height 172 cm (32 percentile), weight 66 kg
- GEN: well-appearing and slim man
- HEENT: EOMI. PERRLA. No scleral icterus.
- Resp: CTAB. No w/r/r.
- CV: RRR. No m/r/g. No peripheral edema.
- GI: active BS, abdomen is soft, non-distended, non-tender. No hepatosplenomegaly
- Lymph: no lymphadenopathy
- Neuro: A&Ox3. no focal deficit.
- Psych: Appropriate mood and cooperative.

LABS





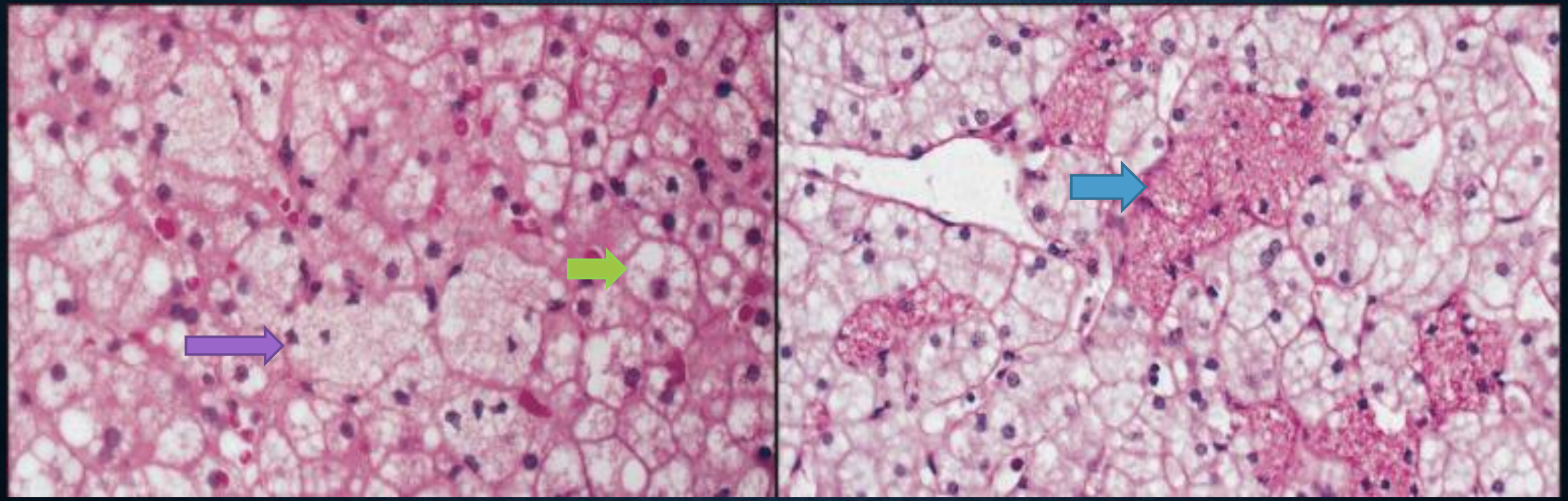
AST 78 [<40]
ALT 115 [<40]
ALP 148 [40-125]
gGTP 36 [<65]
T bili 2.4 [0.3-1.2]
Albumin 4.8

Total cholesterol 345 [135-168]
HDL 30 [39-52]
LDL 289 [80-109]
Triglycerides 130 [53-88]

ADDITIONAL WORK UP

- Chronic liver disease panel was unremarkable
- MRI abdomen showed non-cirrhotic liver without fatty infiltrate, minimal hepatosplenomegaly
- Percutaneous liver biopsy was then pursued…

PERCUTANEOUS LIVER BIOPSY



H&E

PAS-D

THOUGHTS?

- Differential diagnosis?
- Additional work up?

DIFFERENTIAL DIAGNOSIS

- Cholesteryl ester storage disease
- Wolman disease
- Niemann-Pick disease
- Gaucher disease
- Chanarin Dorfman syndrome
- Gangliosidosis
- Mauriac syndrome (poorly controlled type 1 diabetes)
- Non-alcoholic fatty liver disease

WORK UP CONTINUES

- Liver biopsy report
  - Diffuse microvesicular steatosis with swollen Kupffer cells and containing lipidic material

- Skin biopsy for fibroblast culture
  - Acid lipase activity 2 pmol/min/mg protein [50-220]
  - Cholesterol esterification 15.2% of normal control cells [abnormal <10%]

CHOLESTERYL ESTER STORAGE DISEASE

WOLMAN DISEASE & CHOLESTERYL ESTER STORAGE DISEASE

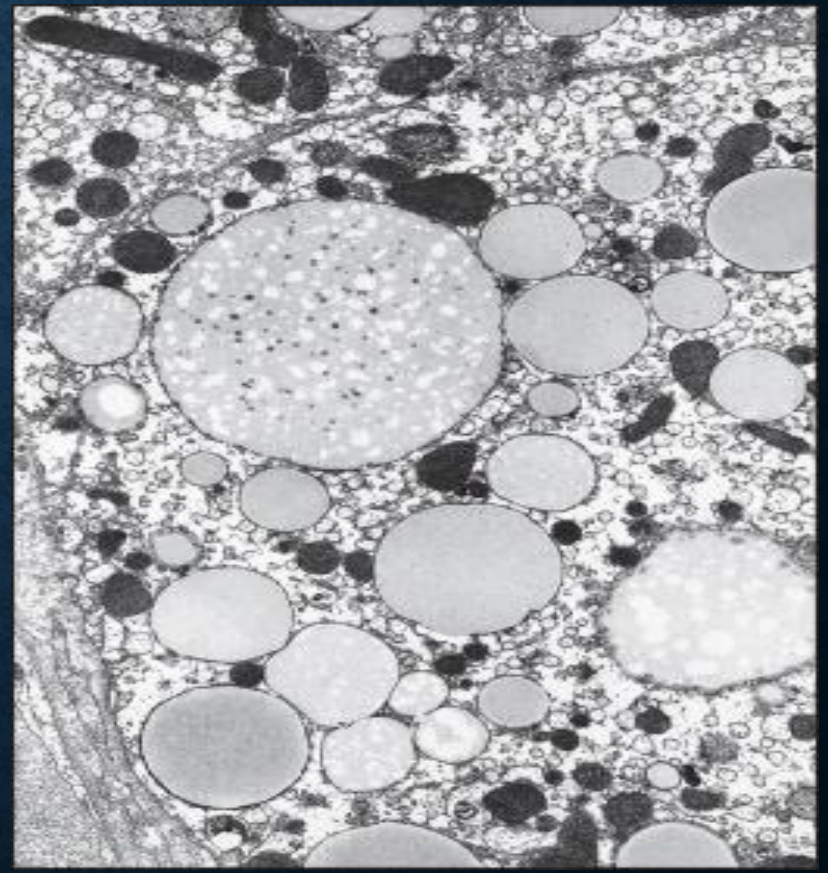
- Lysosomal acid lipase deficiency (LALD)
  - Autosomal recessive disease caused by *LIPA* mutations that encodes acid lipase
    - Un-degraded cholesteryl esters and triglycerides accumulate
  - Wolman disease is more severe than cholesteryl ester storage disease due to complete absence of enzyme lysosomal acid lipase
- Wolman disease
  - May present with hydrops fetalis or congenital ascites
  - Usual presentation include failure to thrive, vomiting, severe diarrhea with steatorrhea
  - Death usually occurs in the first year of life despite aggressive nutritional support

CHOLESTERYL ESTER STORAGE DISEASE (CESD)

- Milder form of the disease (some residual acid lipase function)
- Clinical presentations
  - Presents at any age with hepatomegaly, usually caused by lipid retention in hepatocytes and Kupffer cells
  - In children, diarrhea may occur because of lipid retention in enterocytes leading to malnutrition and short stature
  - Typical nature history of CESD includes premature atherosclerosis and progressive liver disease resulting in cirrhosis
- Labs include elevated aminotransferases, cholesterol, LDL, triglycerides

CHOLESTERYL ESTER STORAGE DISEASE (CESD)

- Likely underdiagnosed, estimated incidence 1 in 40,000
  - Commonly misdiagnosed as non-alcoholic fatty liver disease
- Liver biopsy showing typical findings of CESD
  - Hypertrophied and foamy Kupffer cells
  - Hepatocytes showing microvesicular steatosis
  - Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissue are visualized under polarized light
  - Electron micrograph shows triglyceride droplets of varied size. "moth – eating" appearance
- Microscopic findings guide direct enzymatic testing, but not independently diagnostic
  - Fibroblast culture, peripheral leukocyte, liver tissue - acid lipase activity
  - *LIPA* gene mutation analysis



CHOLESTERYL ESTER STORAGE DISEASE (CESD) - TREATMENT

- Hypolipidemic diet
- Cholesterol reduction strategies
  - HMG-COA reductase inhibitor – Statins
  - Other hypolipidemic agents such as fibrates, cholestyramine and ezetimibe can be used
  - Variable results with some improvement in cholesterol; available cases developed fibrosis progression
- Enzyme replacement therapy (2015)
  - Sebelipase alfa (Kanuma) is a recombinant human LAL protein
  - 20 weeks of IV ERT resulted in normalization of transaminase and improvement in abnormal lipid profile and hepatomegaly
  - Infant – 1 mg/kg weekly up to 3 mg/kg weekly; adult – 1 mg/kg every other week
- Liver transplantation

FOLLOW UP

- After his diagnosis, he was placed on lovastatin 10 mg later changed to rosuvastatin 10 mg daily
- Patient now is 32, BMI 27
  - AST 103, ALT 174, T bili 2, Cholesterol 429, TG 23, HDL 29, LDL 353
  - Ultrasound shows fatty infiltrate, non-cirrhotic liver
  - OSH Liver biopsy showed mild steatohepatitis, fibrosis stage 3 of 4
  - Continue rosuvastatin
- Enzyme replacement therapy?

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TRIVIA
TIME!

WHAT WAS THE YEAR WHEN ENZYME REPLACEMENT THERAPY WAS FIRST USED IN CLINICAL PRACTICE AND FOR WHAT CONDITION?

- 1986, Fabry disease
- 1991, Gaucher disease
- 1998, Mucopolysaccharidosis type I
- 2000, Pompe disease
- 2002, Mucopolysaccharidosis type I

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YOUR ATTENTION
ANY DOUBT
CONSULT GOOGLE