JUST ANOTHER LFT ABNORMALITY REFERRAL

2019 Annual Update in Medical Hepatology

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12/7/2019
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]  Total cholesterol 345 [135-168]
ALT 115  [<40]  HDL 30  [39-52]
ALP 148  [40-125]  LDL 289  [80-109]
gGTP 36  [<65]  Triglycerides 130 [53-88]
T bili 2.4  [0.3-1.2]
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?
REFERENCES

• Hulkova H, Elleder M. Distinctive histopathological features that support a diagnosis of cholesterol ester storage disease in liver biopsy specimens. Histopathology 2012; 60: 1107-1113.
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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