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Management of Extrahepatic Manifestations of Liver Disease

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Research Support: Gilead, Clinical Area- Viral Hepatitis
Research Support: Intercept (spouse), Clinical Area- NASH
Research Support: Conatus (spouse), Clinical Area- IBD
Speaker Bureau: Gilead (self + spouse), Clinical Area- Viral Hepatitis
Speakers Bureau: AbbVie (self + spouse), Clinical Area- Viral Hepatitis
Speakers Bureau: AbbVie (self), Clinical Area- IBD
Speakers Bureau: Intercept (spouse), Clinical Area- NASH
Objectives

• By the end of this presentation, you should be able to:
  – Identify extrahepatic manifestations (EHM) of liver disease
  – Recognize benign from serious EHM findings
  – Determine a management strategy for common EHM
Case Study

- 57 y/o AAM presents to PCP c/o pruritus with associated raised skin lesions
- SH: Lives alone, unemployed, smokes $\frac{1}{2}$ PPD, drinks socially, uses marijuana weekly
- PMH: HTN, s/p MI 2014 with stent placement x2, KCD stage 2
- Vitals/Stats: BMI 29.2, BP 148/88, HR 73, RR 14
- Exam: Unremarkable except skin lesions
What Is an Extrahepatic Manifestation (EHM)?

- Sign or symptom of underlying liver disease occurring outside of the liver
- Some are serious or life-threatening
- Others offer clinical clues underlying liver disease is present

Why do they occur?
- Hepatocytes are responsible for homeostasis
- Disruptions in homeostasis may lead to clinical effects
- May be direct or indirect

Indramohan & Aoun, 2016.
Cardiovascular
- Arteriovenous shunting
- Peliosis hepatis
- Telangiectasia

Respiratory System
- Pulmonary Fibrosis
- Hepatopulmonary Syndrome:
  - Decompensated liver disease
  - Arterial deoxygenation
  - Intrapulmonary vasodilatation
- Portopulmonary hypertension:
  - Portal hypertension without shunting or vasodilation

Hepatopulmonary Syndrome

- Liver transplantation
- Many experimental therapies: sorafenib, norfloxacin, indomethacin, mycophenolate mofetil, methylene blue
- Transjugular intrahepatic portosystemic shunting (TIPS)

Portopulmonary Hypertension

- Exercise as tolerated
- Diuretic therapy
- Avoid TIPS and β-blockers and Ca-channel blockers
- Liver transplant in patients responsive to pulmonary artery hypertension therapies: ambrisentan and tadalafil, prostacyclins

Soulaidopoulos et al, 2018; Rubin, 2019.
EHM by Organ

Kidneys

- Hepatitis-associated nephropathy
  - Membranoproliferative glomerulonephritis
  - Membranous nephropathy
- Hepatorenal syndrome

Skin

- Jaundice
- Pruritus
- Xanthelasma
- “Bronze diabetes”
- Palmar Erythema
- Hair thinning/loss
- Terry’s nails

## Management

### Renal
- Treat underlying cause (viral hepatitis)
- Monitor for proteinuria and hematuria
- Control hypertension
- Plasmapheresis
- Hemodialysis
- Medication: cyclophosphamide, mycophenolate mofetil, corticosteroids

### Skin
- Treat underlying causes
- Xanthelasma may be surgically removed
- Pruritus: antihistamines, cholestyramine, menthol ointment, rifampin, naltrexone, sertraline
- Salvage therapy for refractory cholestatic pruritus

Nervous System

• Hepatic Encephalopathy
• Encephalomyelitis (HAV)
• Myelopathy (HCV)
• Guillain Barre (HBV, HCV)

Hematologic

• Ecchymoses
• Bleeding

Indramohan & Aoun, 2016.
Management of Hepatic Encephalopathy

- 2014 AASLD Hepatic Encephalopathy Practice Guidelines – 74 pages
  - Grade severity (0-4)
  - Identify & treat precipitating cause
    - Infection, electrolyte imbalance, medication effect, etc.
  - Medications: lactulose, rifaximin, branch chain amino acids, antibiotics, probiotics, zinc
  - Ammonia monitoring is not necessary
Neurologic Management

• Encephalomyelitis – very rare, consultation with neurology needed. Requires supportive care, EEG, LP, brain and spine imaging

• Guillain Barre – also rare, described in HAV, HBV, and HCV. May require IV IG, plasmapheresis, supportive care
EHM by Organ

**Thyroid**
- Hypothyroidism

  **Management**: dietary supplements, nutraceuticals, desiccated thyroid, levothyroxine

**Eyes**
- Sicca Syndrome (Sjogren's Syndrome if autoimmune disorder present)

  **Management**: artificial tears, artificial saliva, immunosuppressants (hydroxychloroquine)

Ko et al. 2012.
Soft Tissue

- Dupuytren’s Contracture

- May be r/t heavy alcohol use, diabetes, male sex over 40, and smoking

- Management: stretching, corticosteroid injections, collagenase clostridium histolyticum injection, low-dose radiation, surgery

EHM & the Immune System

- Cryoglobulinemia
  - Palpable Purpura
  - Vasculitis
  - Nephropathy

Image credit: https://unckidneycenter.org/kidneyhealthlibrary/glomerular-disease/cryoglobulinemia/;
Ko et al. 2012.
Disease Specific EHMs

Hepatitis C Infection

- Accelerated atherosclerosis
- Cardiomyopathy
- Pulmonary Fibrosis
- Peripheral Neuropathy
- Prurigo Nodularis
- Lichen Planus
- Porphyria Cutanea Tarda
- Lymphoma
- Insulin Resistance/Diabetes
- Fatigue
- Depression
- Cognitive Impairment
- Immune system changes

Ko et al. 2012.
NASH
• Accelerated atherosclerosis

Wilson’s Disease
• Psychiatric: personality changes, cognitive dysfunction
• Motor: dyspraxia, ataxia, tremor-rigidity syndrome

Disease Specific EHMs

Primary Biliary Cholangitis
• Autonomic Dysfunction
• Sensory neuropathy
• Fatigue

Primary Sclerosing Cholangitis
• Vitiligo
• Fatigue

Image credit: https://www.dailymail.co.uk/health/article-6230519/Woman-22-refused-accept-deadly-liver-failure-caused-vitiligo-face.html;
Near-Infrared Spectroscopy Reveals Brain Hypoxia and Cerebrovascular Dysregulation in Primary Biliary Cholangitis

Duszynski et al. 2019.
Case Study

- **Labs:** AMA, ANA, EMA, CRP, ESR, CBC, CMP, Viral Hepatitis Panel
- **Results:** autoantibodies all negative
- CRP and ESR mildly elevated
- CBC shows plt 180, WBC 4.8, Hgb 16.1
- CMP shows AST 41, ALT 65, creatinine 1.2
- Viral Panel shows HCV Ab+, reflex HCV RNA 41,800
- Diagnosis: Prurigo Nodularis secondary to chronic HCV infection
6 months later, HCV cure confirmed
Near complete resolution of prurigo nodularis

Photo credit: https://jamanetwork.com/journals/jamadermatology/article-abstract/1216893.
Summary

- EHMs are numerous: close attention on physical exam is important
- EHMs may resolve if underlying cause is treated
- Referrals to specialists may be needed
- Hepatitis C virus infection is a common cause for EHM
  - Direct cytopathic role has been identified in B-cell lymphomas, but most EHMs likely secondary to host immune response

Ko et al. 2012.


