



GHAPP

Gastroenterology & Hepatology
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Management of Extrahepatic Manifestations of Liver Disease

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Disclosures

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Disclosures

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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 EHMs

Case Study

- 57 y/o AAM presents to PCP c/o pruritus with associated raised skin lesions
- SH: Lives alone, unemployed, smokes ½ 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



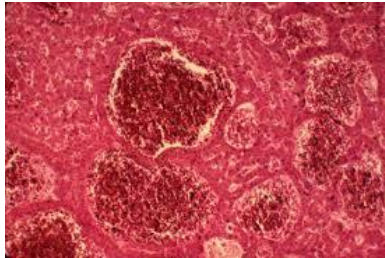
What Is an Extrahepatic Manifestation (EHM)?

- 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

EHM by System

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

Cardiovascular and Respiratory Management

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

EHM by Organ

Kidneys

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

Skin

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



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

EHM by System

Nervous System

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

Hematologic

- Ecchymoses
- Bleeding

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)

EHM by Organ

Soft Tissue

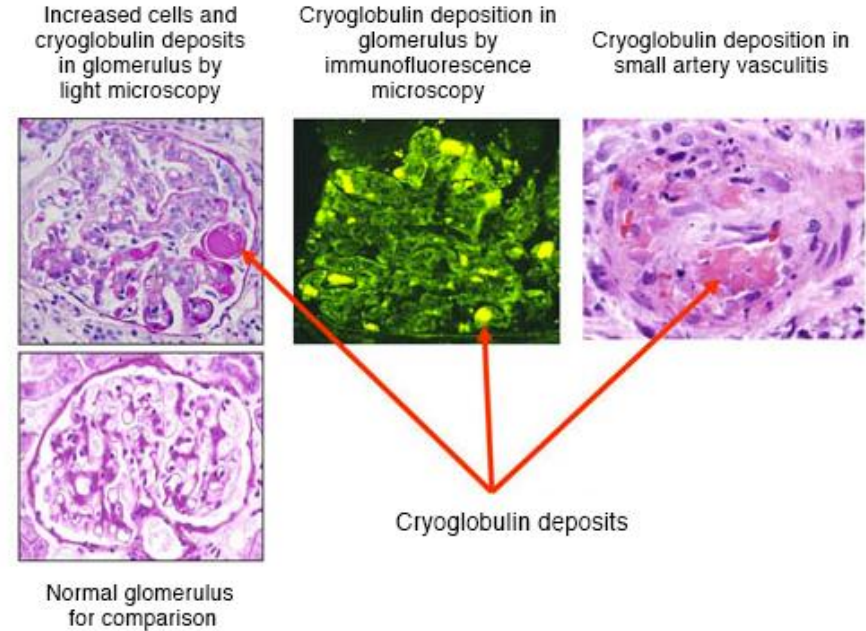
- Dupuytren's Contracture



- 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



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

Disease Specific EHMs

NASH

- Accelerated atherosclerosis

Wilson's Disease

- Psychiatric: personality changes, cognitive dysfunction
- Motor: dyspraxia, ataxia, tremor-rigidity syndrome

Disease Specific EHM's

Primary Biliary Cholangitis

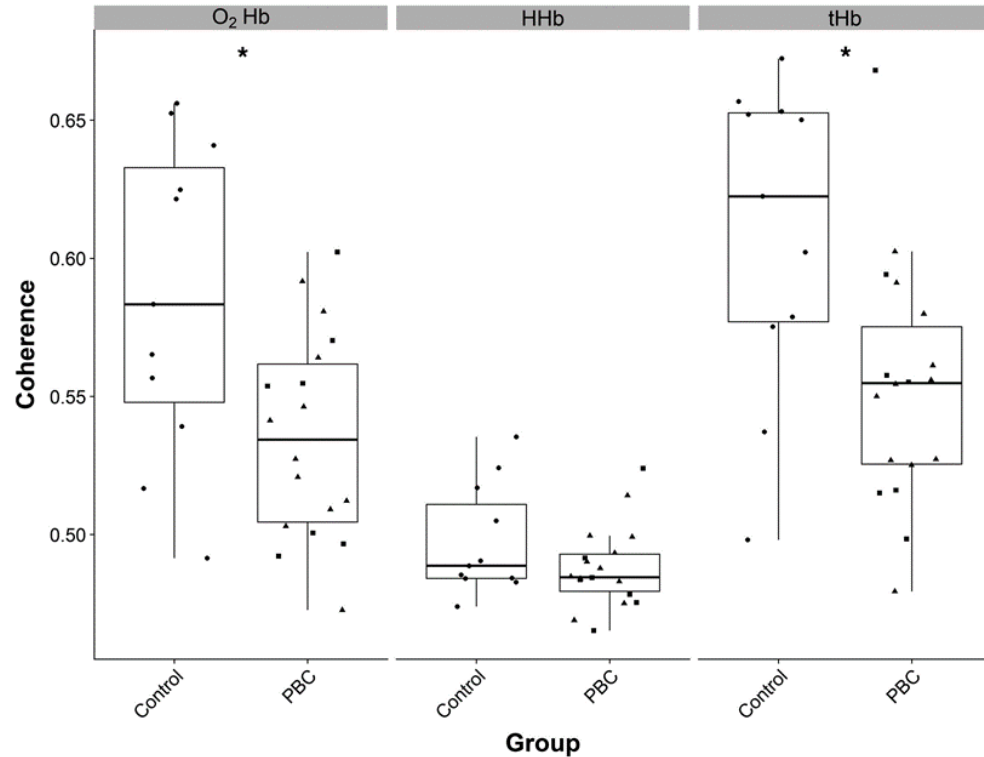
- Autonomic Dysfunction
- Sensory neuropathy
- Fatigue

Primary Sclerosing Cholangitis

- Vitiligo
- Fatigue



Near-Infrared Spectroscopy Reveals Brain Hypoxia and Cerebrovascular Dysregulation in Primary Biliary Cholangitis



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

Case Study

6 months later, HCV
cure confirmed

Near complete resolution
of prurigo nodularis



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

References

- Duszynski, C.C, Avati, V., Lapointe, A.P., Scholkmann, F., Dunn, J.F., & Swain, M.G. (2020). Near-infrared spectroscopy reveals brain hypoxia and cerebrovascular dysregulation in primary biliary cholangitis. *Hepatology* 71(4), 1408-1420. doi: 10/1002/hep.30920
- Hegade, V. S., Kendrick, S. F., & Jones, D. E. (2015). Drug treatment of pruritus in liver diseases. *Clinical Medicine*, 15(4), 351–357.
<https://doi.org/10.7861/clinmedicine.15-4-351>
- Indramohan, P. & Aoun, E. (2016). Extra hepatic manifestations of liver diseases. *Practical Gastro*, XL(3).
<https://practicalgastro.com/2016/03/06/extra-hepatic-manifestations-of-liver-diseases/#:~:text=Arthritis%20maybe%20the%20first%20manifestation,cirrhosis%2C%20autoimmune%20hepatitis%20and%20hemochromatosis.>
- Ko, H.M., Hernandez-Prera, J.C., Zhu, H., Dikman, S.H., Sidhu, H.K., Ward, S.C., & Thung, S.N. (2012). Morphologic features of extrahepatic manifestations of hepatitis C virus infection. *Journal of Immunology Research* 2012. doi: 10.1155/2012/740138
<https://www.hindawi.com/journals/jir/2012/740138/>
- Ozkok, A., & Yildiz, A. (2014). Hepatitis C virus associated glomerulopathies. *World Journal of Gastroenterology*, 20(24), 7544–7554.
<https://doi.org/10.3748/wjg.v20.i24.7544>
- Rubin, L.J. (2019). Portopulmonary hypertension. *Up-to-Date*. Accessed September 23, 2020 from <https://www.uptodate.com/contents/portopulmonary-hypertension#H21>
- Soreide, M.H., Murad, J.M., Denbeigh, E.A., Lewallen, A., Dudakovic, L...& Kakar, S. (2018). Treatment of Dupuytren's contracture. *The Bone & Joint Journal*, 100-B(9), 1138-1145. doi.org/10.1302/0301-620X.100B9.BJJ-2017-1194.R2
- Soulaidopoulos, S., Cholangitis, E., Giannakoulas, G., Vlachou, M., & Goulis, I. (2018). Review article: Update on current and emergent data on hepatopulmonary syndrome. *World Journal of Gastroenterology*, 24(12), 1285–1298.
<https://doi.org/10.3748/wjg.v24.i12.1285>