
# GHAPP

Gastroenterology & Hepatology
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Annenberg Center For Health Sciences at Eisenhower
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# Cholestatic Disease

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# Disclosures

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Speakers Bureau: Salix, Clinical Area: Hepatic Encephalopathy

# KK Case Presentation

- KK is a 70-year-old female patient with past medical history of hypertension and diabetes type 2.
- She was treated with Nitrofurantoin for UTI a week ago.
- Presented to the ED with painless jaundice started 3 days ago.
- Denies any fever, chills, SOB, altered mental status or any signs of GI bleeding, such as melena hematochezia or hematemesis.
- VSS.
- PE: NAD; Alert and oriented x 3; jaundiced.

# KK Laboratory Test

- CBC
  - Platelets 160; WBC 6.5
- PT/INR
  - INR 1.5
- BMP
  - Creatinine 1.0
- Hepatic panel
  - AST 840
  - ALT 1045
  - TB 15
  - TP 5.6
  - Alb 4.2

# KK Laboratory Test

- Blood/urine cultures (-)
- Viral hepatitis (A, B,C, E) (-); HSV, VZV, EBV,CMV, PARVO (-)
- Autoimmune panel
  - ANA (+) 1:30
  - ASMA (-)
  - Anti LKM (-)
- Gammaglobulins (-)
- MELD- Na 25

# KK Imaging

- US abdomen
  - The liver appears normal
  - Extrahepatic ducts normal in caliber; no intrahepatic bile duct dilatation
  - Spleen is normal in size and appearance
  - Both kidneys are normal in size; no hydronephrosis
  - Aorta is normal in caliber
- Liver biopsy

# KK Histological Features

- Portal inflammation
- Absence of fibrosis
- Portal neutrophils/plasma cells and intracellular cholestasis

# KK Differential Diagnosis

- Immune mediated DILI
- DILI-induced AIH
- AS-AIH
- AS-AIH with ALF

# KK Diagnosis and Treatment

## DILI-induced AIH

- Drug intake triggers an immune process which leads to the development of chronic AIH
- Patients may present with serological and/or histological markers of idiopathic AIH
- Long-term immunosuppression is usually required

# KK Diagnosis and Treatment

## DILI-induced AIH

- Portal inflammation, absence of fibrosis, portal neutrophils/plasma cells and intracellular cholestasis are more suggestive of DILI than idiopathic AIH
- Discontinuation of the causative agent usually induces spontaneous resolution
- Corticosteroids with prednisone 40-60 mg per day orally
- Patient condition improved, tapered prednisone dose to 5 mg PO per day lifelong; monitor labs

# BB Case Presentation

- BB is a 30-year-old female patient who is otherwise healthy presented to the ED with anorexia, jaundice, ascites and altered mental status
- According to family member, the patient symptoms started last week with RUQ abdominal pain and noticed to be jaundiced
- No fever, chills, SOB or any signs of GI bleeding,  such as melena, hematochezia or hematemesis
- VS: Tachycardic at 120’s; BP 100/70; RR 18; O2 sat 98% RA
- PE: Confused to time, person and place; jaundiced. Abdomen soft; non tender + asterixis

# BB Laboratory Test

- CBC
  - Platelets 100; WBC 7.5
- PT/INR
  - INR 2.5
- BMP
  - Creatinine 1.0
- Hepatic panel
  - AST 998
  - ALT 1077
  - TB 22
  - TP 5.6
  - Alb 3.4

# BB Laboratory Test

- Blood/urine cultures (-)
- Viral hepatitis (A, B,C, E) (-); HSV, VZV, EBV,CMV, PARVO (-)
- Autoimmune panel
  - ANA (+) 1:80
  - ASMA (-)
  - Anti LKM (-)
- Gammaglobulins- N
- MELD- Na: 34

# BB Imaging

- US abdomen
  - The liver appears normal
  - Extrahepatic ducts normal in caliber; no intrahepatic bile duct dilatation
  - Spleen is normal in size and appearance
  - Both kidneys are normal in size; no hydronephrosis
  - Aorta is normal in caliber
- Liver biopsy

# BB Imaging

- Computed Tomography (CT)
  - Heterogenous hypo-attenuated regions within the liver
  - No PH
  - No mass

# BB Histological Features

Portal inflammation with interface; interface between portal tract and hepatic parenchyma, with moderate activity associated with conspicuous plasma cell component.

There’s lobular hepatitis with disarray of the liver cell plates. Diffuse necro-inflammatory activity and regenerative hepatocellular resetting.

# BB Differential Diagnosis

Immune mediated DILI

DILI-induced AIH

AS-AIH

AS-AIH with ALF

# BB Diagnosis and Treatment

## AS-AIH with ALF

- The absence of pathognomonic features makes the diagnosis of AS-AIH challenging and one of exclusion.
- The potential complications of corticosteroid therapy necessitate thorough exclusion of alternative causes of acute severe hepatitis, including viral hepatitis, toxins, DILI, ischemia and metabolic disorders.

# BB Diagnosis and Treatment

AS-AIH with ALF

- Symptoms management
  - HE
- Liver Transplantation evaluation

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# Autoimmune Hepatitis

# Background

- Autoimmune Hepatitis
  - Rare
  - Immune mediated
  - Inflammatory condition
  - Characterized by circulating autoantibodies
  - Hypergammaglobulinemia
  - Distinctive features in liver biopsy

# Clinical Presentation

- Heterogenous and can vary from asymptomatic disease to liver failure requiring LT
- Diagnostic uncertainty with wide spectrum of presentations
- Absence of pathognomonic features
- Variability in treatment response

# Clinical Presentation

- Anorexia, jaundice, ascites and HE are more likely to be present in patients with acute severe forms of AIH (regardless of underlying cirrhosis/fibrosis status)
  - Bilirubin
  - ALT
  - AST
  - Gamma-globulins
  - INR
  - MELD scores

*Increased in acute and severe presentations of AIH, but not specifically AS-AIH (±ALF)

# Serology

- Autoantibodies are diagnostically useful in the acute presentations of AIH:
  - Type 1 AIH:
    - Anti-nuclear antibody (ANA)
    - Anti-smooth muscle antibody (ASMA)
    - Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)
  - Type 2 AIH:
    - Anti-liver kidney microsomal-1 and 3
    - Anti-LKM 1 and 3
    - Anti-liver cytosol-1 antibody (anti-LC-1)

# Serology

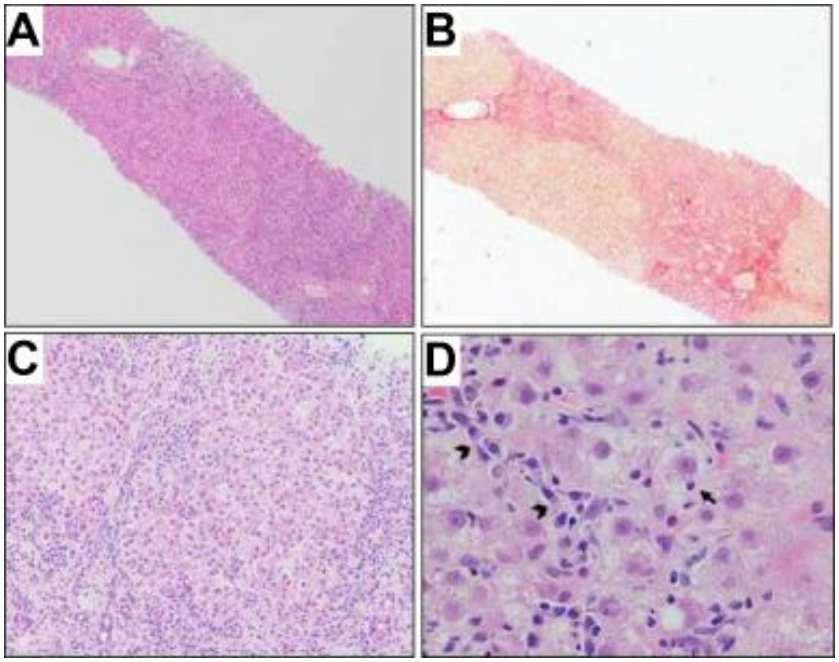
- If clinical suspicion is high:
  - Autoantibody results should not delay biopsy (or corticosteroid initiation)
  - In cases of seronegativity, it is worth requesting an extended autoantibody screen (including anti-SLA/ LP) as the conventional panel usually includes ANA, ASMA and anti-LKM. We also recommend repeating serology
- Autoantibodies should be interpreted by caution as it can yield false positive results:
  - 20–30% of patients with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis can have positive ANA
  - ANA, ASMA, and LKM can be positive in HCV pts

# Imaging

- Liver ultrasound
- Computed Tomography
- MRI

# Histological Features DILI-Induced AIH

A. Severe liver damage with areas of bridging necrosis and post-necrotic collapse




B. The hepatic parenchyma shows nodular configuration secondary to post-necrosis collapse, no obvious fibrosis or early collagen deposition

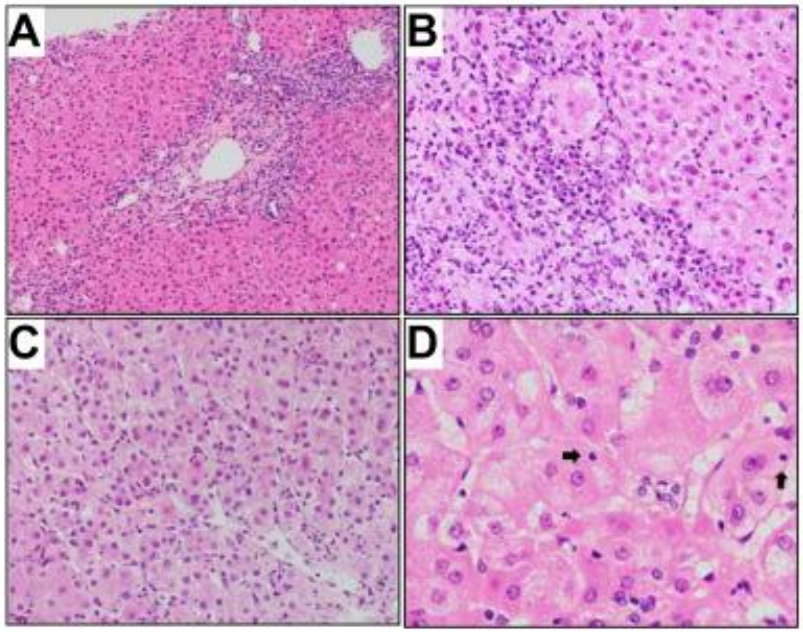
C. Lobular disarray with multiple necro-inflammatory foci and reactive changes of the liver cell plates with regenerative rosettes

D. Detail of an inflammatory area with clusters of plasma cells, hepatocyte reactive changes with cell ballooning and focal emperipolesis

Musarat, et al. 2020.

# Typical Histological Features AS-AIH With ALF

A. Portal inflammation with interface




B. Detail of the interface between portal tract and hepatic parenchyma, with moderate activity associated with conspicuous plasma cell component

C. Lobular hepatitis with disarray of the liver cell plates. Diffuse necro-inflammatory activity and regenerative hepatocellular resetting

D. Occasional emperipolesis activity. Intracytoplasmic lymphocytes are spotted in some hepatocytes

Musarat, et al. 2020.

# Histology

- Typical histological features of AIH may not be present early or during an acute de novo presentation
- Liver biopsy is crucial in making the dx and must be sought in earliest opportunity
- Appropriate histological interpretation and useful background clinical information (time frame from onset of symptoms and potential viral/drug exposures)

# Histology

- Acute forms of AIH predominantly affect the centrilobular zones
- Centrilobular necrosis in the acute presentations of AIH may reflect the stage preceding portal involvement (disease severity)
- It is not specific to an acute presentation and can be found in chronic AIH or acute on chronic
- Central perivenulitis, which is characterized by lymphoplasmacytic infiltration surrounding the central vein (with centrilobular necrosis, lymphoid aggregates and plasma cell-enriched infiltration)

# Criteria for Autoimmune-ALF

- Central perivenulitis
- Lymphoid aggregates
- Plasma cell enrichment
- Type 4* or 5** MHN
  - MHN- Massive hepatic necrosis
  - *Type 4 MHN = pan-lobular necrosis, prominent centrilobular necro-inflammation and hemorrhage
  - **Type 5 MHN = classical peri-portal AIH in conjunction with super-imposed changes of massive necrosis ± centrilobular necro-inflammation

# Criteria for Autoimmune-ALF

- Assessment of fibrosis can differentiate between acute and chronic AIH
- Challenges in distinguishing true fibrosis from post-necrotic collapse
- Special stains to assess the liver architecture and connective tissue composition are of great importance to avoid overestimation of fibrosis (Masson’s trichrome or Picrosirius red)

# Definitions

- Acute liver failure (ALF)
  - Includes evidence of coagulopathy and any degree of hepatic encephalopathy (HE) within 26 weeks of the onset of illness in a patient without pre-existing cirrhosis
  - Subcategorized with length of illness:
    - “Hyper-acute” (<7 days)
    - “Acute” (7–21/28 days)
    - “Subacute” (>21 days and <24/26 weeks)

# AIH Definitions

For patients with acute presentation (<26 weeks):

- Acute-icteric AIH: icteric with no evidence of coagulopathy or encephalopathy
- AS-AIH: icteric and coagulopathic (INR 1.5), but no evidence of encephalopathy
- AS-AIH with ALF: icteric, coagulopathic (INR >−1.5) and encephalopathic

# KK Diagnosis and Treatment

- Other forms of AIH and DILI:
  - AIH with superimposed DILI: pre-existent chronic AIH (±advanced fibrosis) with additional DILI insult
  - Immune-mediated DILI: drug intake triggers AIH (limited time course);
  - Serological and/or histological markers of idiopathic AIH
  - Spontaneous remission after drug cessation and steroid withdrawal
- Difficult to distinguish clinically, serologically and histologically from idiopathic AIH

# AS-AIH Without ALF

- <26 weeks indicates the time between the development of jaundice and coagulopathy
- Confirmation of AS-AIH may only be possible after biopsy or explant analysis
- Stratification of patients into the above categories may influence management and prognostication

# Acute-on-Chronic Liver Failure and AIH

- Acute-on-chronic liver failure (ACLF) is a clinical syndrome of acute hepatic decompensation with superimposed acute injury observed in patients with pre-existing cirrhosis characterized by the presence of extrahepatic organ failure
- Precipitating factors include heavy alcohol intake, viral hepatitis, drugs, AIH, ischemic hepatitis, infection/sepsis and hemorrhage

# Acute-on-Chronic Liver Failure and AIH

Patients with acute presentations of AIH, Wilson's disease, HBV and Budd-Chiari syndrome can be included in the definition of ALF, despite the possibility of underlying chronic liver disease

# Approach to Treatment

## Corticosteroids

- Corticosteroid responsiveness is a defining/diagnostic feature of AIH
- Biochemical remission rates likely to be in the region of 60–80% at 6 months
- AS- AIH response rates are more variable (36–100%)
- Induction regimens included prednisolone (1.5 mg/kg/day) or 3 days of Methyl- prednisolone (1 g/day) with a subsequent prednisolone dose
- Additional immunosuppression (corticosteroids/cyclosporine of tacrolimus/MMF)
- AS-AIH with features of ALF, potentially at the point of irreversibility, thus making corticosteroid therapy futile (one study pt died of disseminated aspergillosis)

# Predictors of Corticosteroid Failure at Presentation

For patients with AS-AIH and HE, it is crucial to identify those that may respond to corticosteroids and those that would benefit from immediate LT

- Bilirubin and INR levels at presentation may predict corticosteroid response
- Presence of low grade HE and absence of MHN on histology may be associated with corticosteroid response
- MELD scores <27
- Hyperbilirubinemia and presence of HLA DRB1*03 may predict corticosteroid failure (Mayo)

# Assessing Response Once Corticosteroids Have Started

- Transaminase activity – not
- Bilirubin and INR
  - Failure to improve pre-treatment hyperbilirubinemia after 2 weeks of corticosteroid therapy was invariably associated with early mortality
  - Acute (±chronic) liver failure

# Change in Prognostic Indices

- Failure to improve MELD-Na scores within 7 days of corticosteroid therapy indicates a high risk of progressing to ALF
- If the point of corticosteroid rescue has passed and there is no improvement in bilirubin, INR/PT or MELD-Na after 7 days of corticosteroid therapy, continuing them may be futile and patients should be assessed for LT immediately

# Liver Transplantation

- Only effective therapy for some patients with AS-AIH and AIH- ALF
  - LT should not be delayed by protracted courses of corticosteroids
  - In practice, simultaneous transplant assessment should run parallel to a trial of corticosteroids
- Histological examination of the explanted liver and correlation with pre-transplant serology provides useful information to the transplant team
- Elevated liver enzymes and immunoglobulins before LT, + lymphoplasmacytic infiltration with moderate to severe inflammatory activity in explants, may be associated with a greater probability of recurrent AIH post-transplantation
- Many advocate the use of long-term corticosteroids post-transplantation to prevent rejection and recurrent disease

# Conclusion

- Careful patient selection is important in ensuring corticosteroid success
- If a patient has acute-icteric hepatitis or AS-AIH, there is a reasonable probability that they will respond to a trial of corticosteroids
- Assessment of response is required after the initiation of therapy, to evaluate the need for LT
- The development of HE and other features of ALF, make response to corticosteroids less likely

# Conclusion

- There is a need for reliable prognostic predictors to facilitate patient selection for LT
- If the point of corticosteroid rescue has passed and there is no improvement in bilirubin, INR/ PT or MELD-Na after 7 days of corticosteroid therapy, continuing them may be futile and patients should be assessed for LT immediately
- For the sickest cohort (e.g. those with HE), assessment at day 3 of corticosteroid therapy requires further evaluation

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# Q&A

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