CRYPTO CAN BE CONFUSING: CIRRHOSIS OCCURRING IN HETEROZYGOUS A1AT DEFICIENCY

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KEY POINTS

- Autosomal co-dominant disease characterized by missense mutations in SERPINA1 gene, resulting in accumulation of polymerized protein within the Endoplasmic reticulum of hepatocytes
- Prevalence : Highest in Northern Europe, 1:2000
- 116 million Carriers, 3.4 million deficient individuals
- Males > Females – studies showing hormonal effects contribute to increased expression of A1AT
- A1AT is also an acute phase reactant
- Over 90 Variants of alleles, M/S/Z most common alleles
- M – normal, Z and S are abnormal
- M allele in heterozygous state can manifest as mutant M allele (M Duarte/M Malton)
- ZZ is the homozygous variant associated with severe deficiency, causing emphysema, chronic hepatitis, and decompensated cryptogenic cirrhosis, associated with marked clinical variability
- Endoplasmic stress response: ER associated degradation can protect affected cells and remove mutant protein
- Apoptosis driven disease, elevation in liver enzymes may not accurately depict severity of disease
- Theoretically plasma concentration of A1AT is inversely proportional to risk of disease

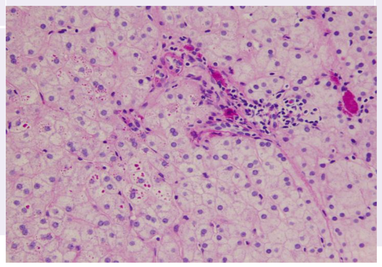
CASE DESCRIPTION

HPI	• 47 Y F with PMHx of HTN, found to have elevated liver enzymes, after hysterectomy with bleeding complications. She presents to the GI clinic with complaints of abdominal distention, change in sleep habits, brain fog, and difficulty gathering thoughts and completing sentences
Social Hx **Medication Hx** **Family Hx**	• No Alcohol, Tobacco, Recreational drugs • Diamox for Ascites • Mother – Pancreatic Ca, Father - Cirrhosis

LABS	06/2021	10/1/2021
Hep A IgM	NEGATIVE	
Hep B Core Total Ab	NEGATIVE	
Hep B S Ag	NEGATIVE	
Hep C Ab	NEGATIVE	
Hep C Viral Load	NEGATIVE	
HIV 1/2 Ag	NEGATIVE	
Transferrin		260
Ceruloplasmin	25	
AST	27	21
ALT	45	33
GGT	80	39
ALP	77	85
S. Creat	1.2	2.5
T. Bili	0.4	0.4
Sodium	138	134
INR	1.06	0.9
MELD-NA	9	17

ANA	Negative
Smooth muscle antibody	Negative
Anti- Liver/Kidney microsomal antibody	Negative
Alpha 1 Antitrypsin Phenotype	MZ
Alpha 1 Antitrypsin	104
IgG	1200
Mitochondrial Antibody	<0.1

Liver Biopsy



- Portal and minimal periportal fibrosis present, stage 1-2
Patchy intracytoplasmic inclusions of PAS-D positive spherical globules in periportal hepatocytes, consistent with heterozygous mutation for alpha-1-antitrypsin deficiency

Ultrasound CT abdomen	Parenchymal changes suggestive of Cirrhosis Subtle nodular changes to contour suggestive of Cirrhosis
Treatment	Transplant Hepatology Evaluation >> Liver Transplant on 11/2021 Complications at Time of transplant: Hepatic Artery redo anastomosis, Donor with +Blood cultures (Bacteroides) Patient started on Tacrolimus

REVIEW OF STUDIES

- Single center retrospective study showed prevalence of MZ genotype being higher in patients with higher MELD-Na Scores, decompensation of cirrhosis with ascites or encephalopathy was significantly more frequent in patients with MZ than MM
- MZ patients with hypotransferrinemia (<180), or increased Tf saturation are at higher risk of death and liver transplantation
- Retrospective analysis from referral centers report 2-5-fold increase of PiMZ in patients with CLD, Cirrhosis, and concurrent viral hepatitis
- PiZ allele carriers with hepatitis C, CF, hemochromatosis are likely to progress or present with advanced cirrhosis
- Normal plasma concentration of A1AT does not exclude Z,S, and does not exclude presence of Z Protein Accumulation

DISCUSSION

- Our patient's presentation is unique as they developed cirrhosis in the absence of other socio-environmental, infectious, and autoimmune risk factors.
- This patient did not have any lung symptoms or findings suggestive of A!AT deficiency
- Liver biopsy is indicative of liver injury secondary to A1AT deficiency
- Some questions to ask ourselves?
  - Was there polymerization of the normal M allele in the presence of Z allele
  - Apart from commonly known hepatic insults, could there be something additional contributing to the Endoplasmic stress response?
  - Is screening for A1AT a viable option, the average test costs between 60-100 dollars, WHO recommends screening patients with COPD
- Benefits of identifying carriers:
  - Early genetic counseling
  - Education to prevent further lung/liver insult or injury
  - Transplant assessment

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