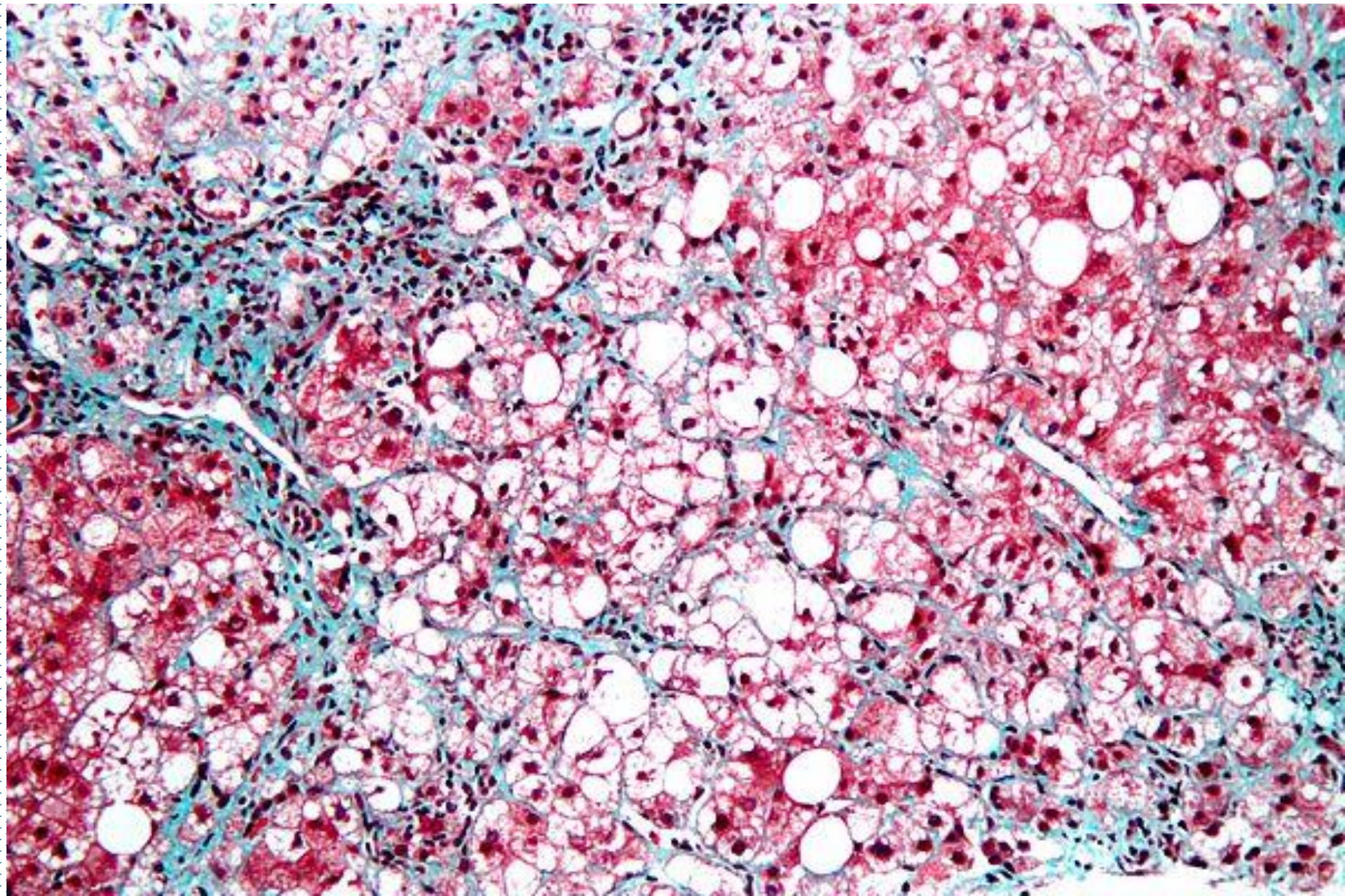


Fatty Liver

Tir 1405



- **Fat accumulation in hepatocytes alone:**

liver steatosis

Accompanied with inflammation:

Steatohepatitis

- Fatty infiltration is typically defined as fat >5% of the liver by imaging, direct quantification, or histologic estimation.

- **Alcohol = Alcoholic Steatohepatitis (ASH).**
- **Metabolic Dysfunction-Associated Steatohepatitis (MASH).**
 - **Previously *non-alcoholic steatohepatitis* (NASH).**[\[2\]](#)

Histopathology

- **Steatosis (usually macrovesicular) - key feature.**
 - If less than 10% ... consider alternate diagnosis/disease process.

- **Hepatocyte injury:**

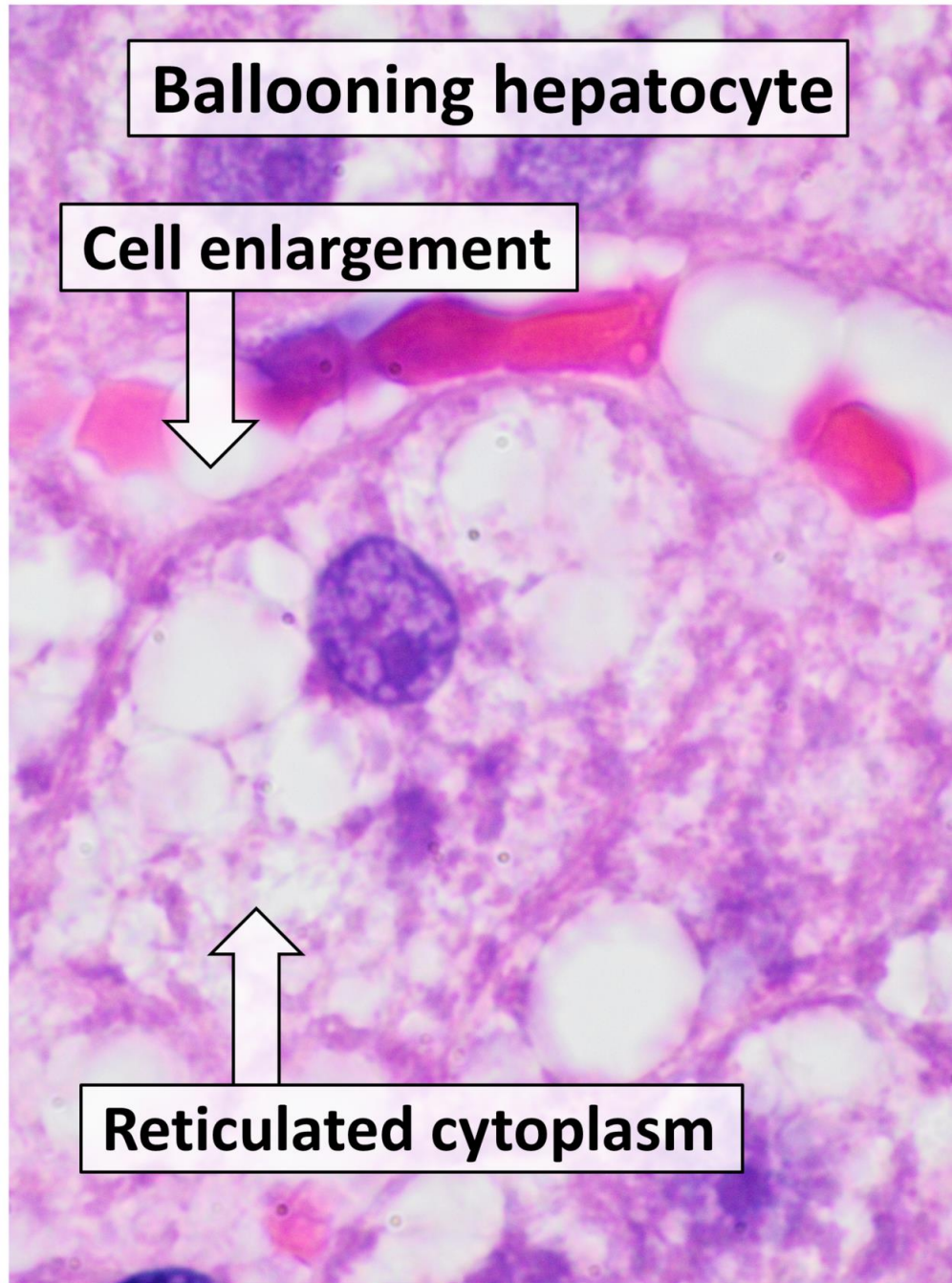
- [Ballooning degeneration](#) - key feature. †
- Mallory bodies.
 - Mallory body wannabes: "occasional cytoplasmic clumping".

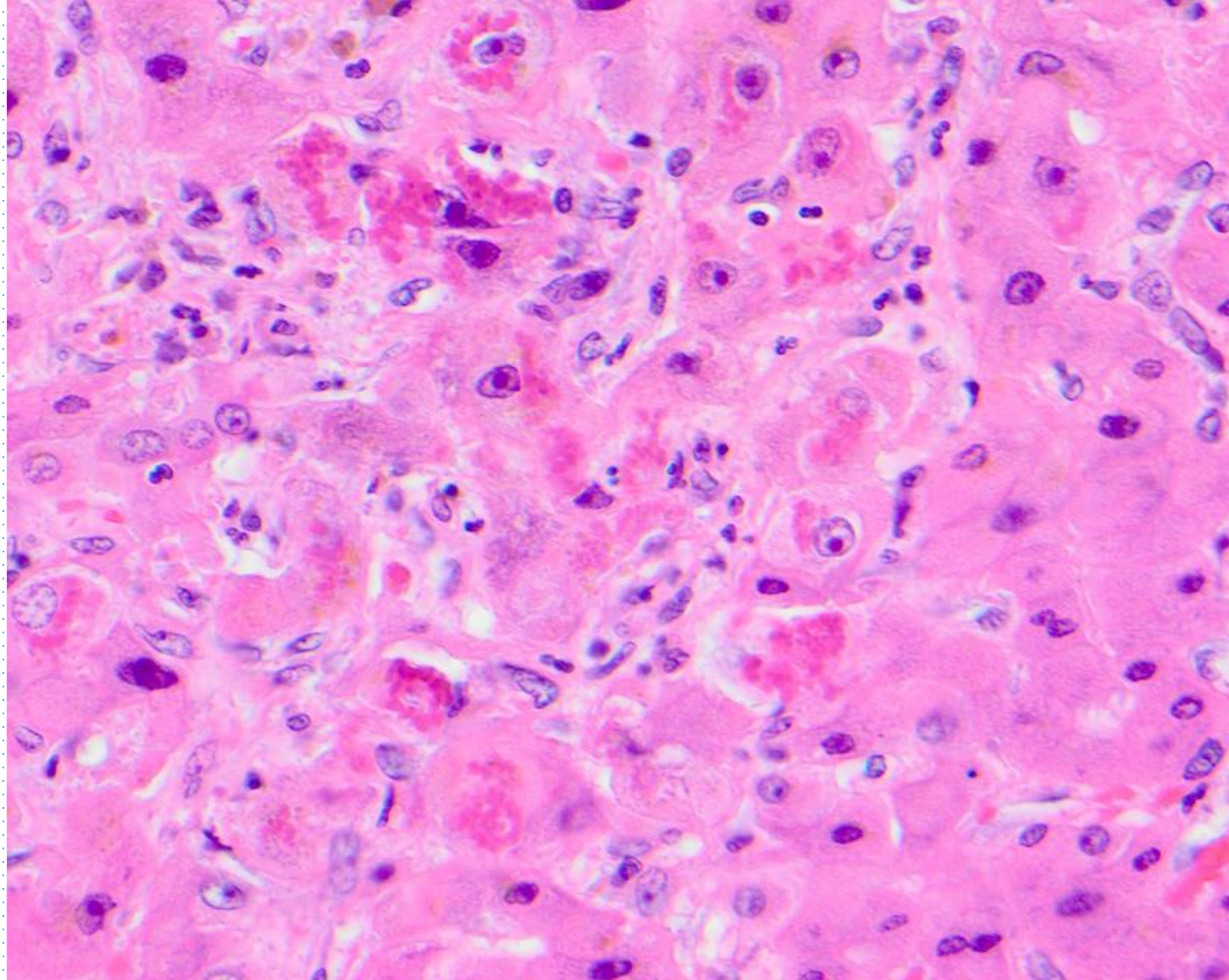
Ballooning hepatocyte

Cell enlargement



Reticulated cytoplasm



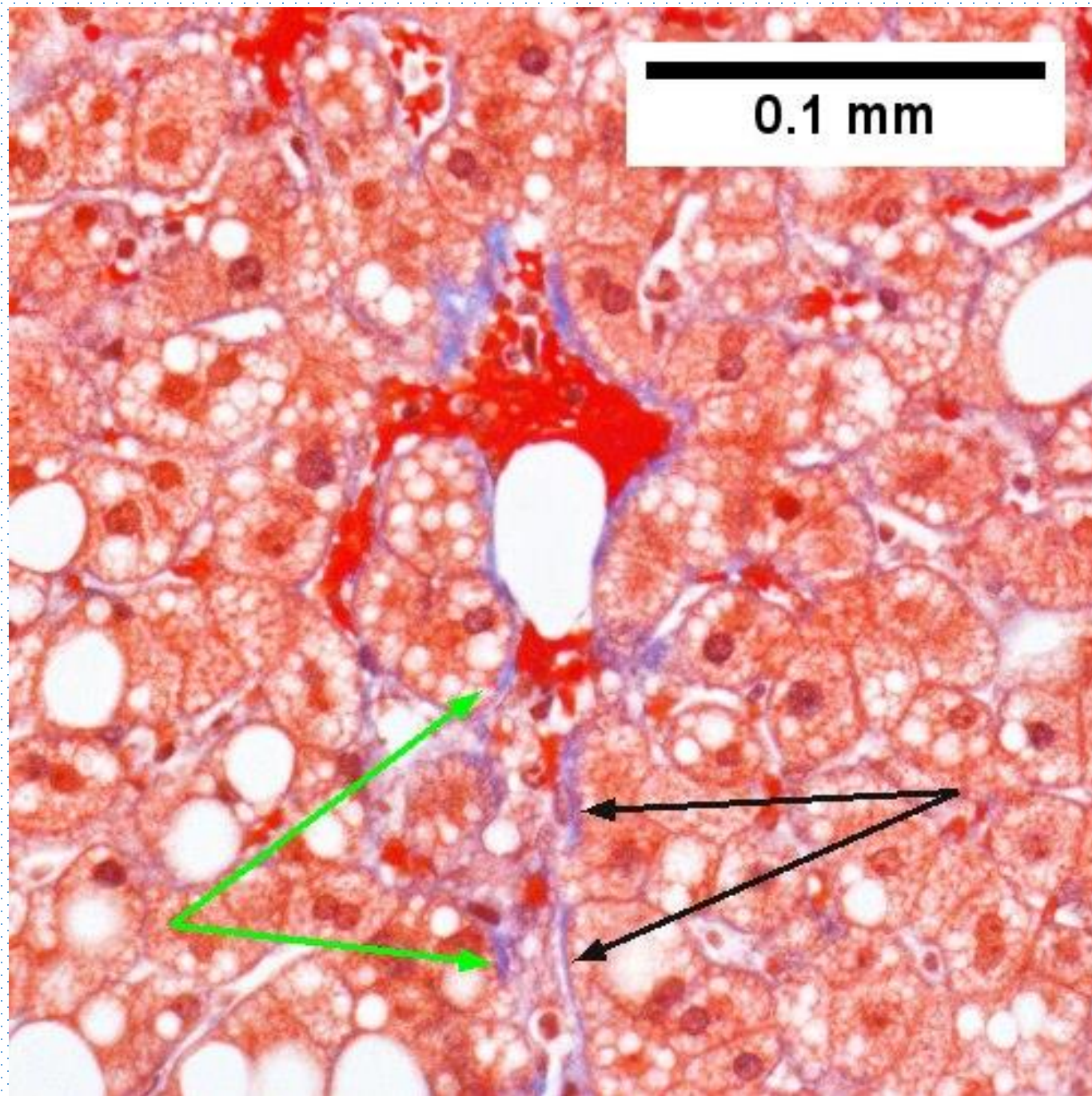


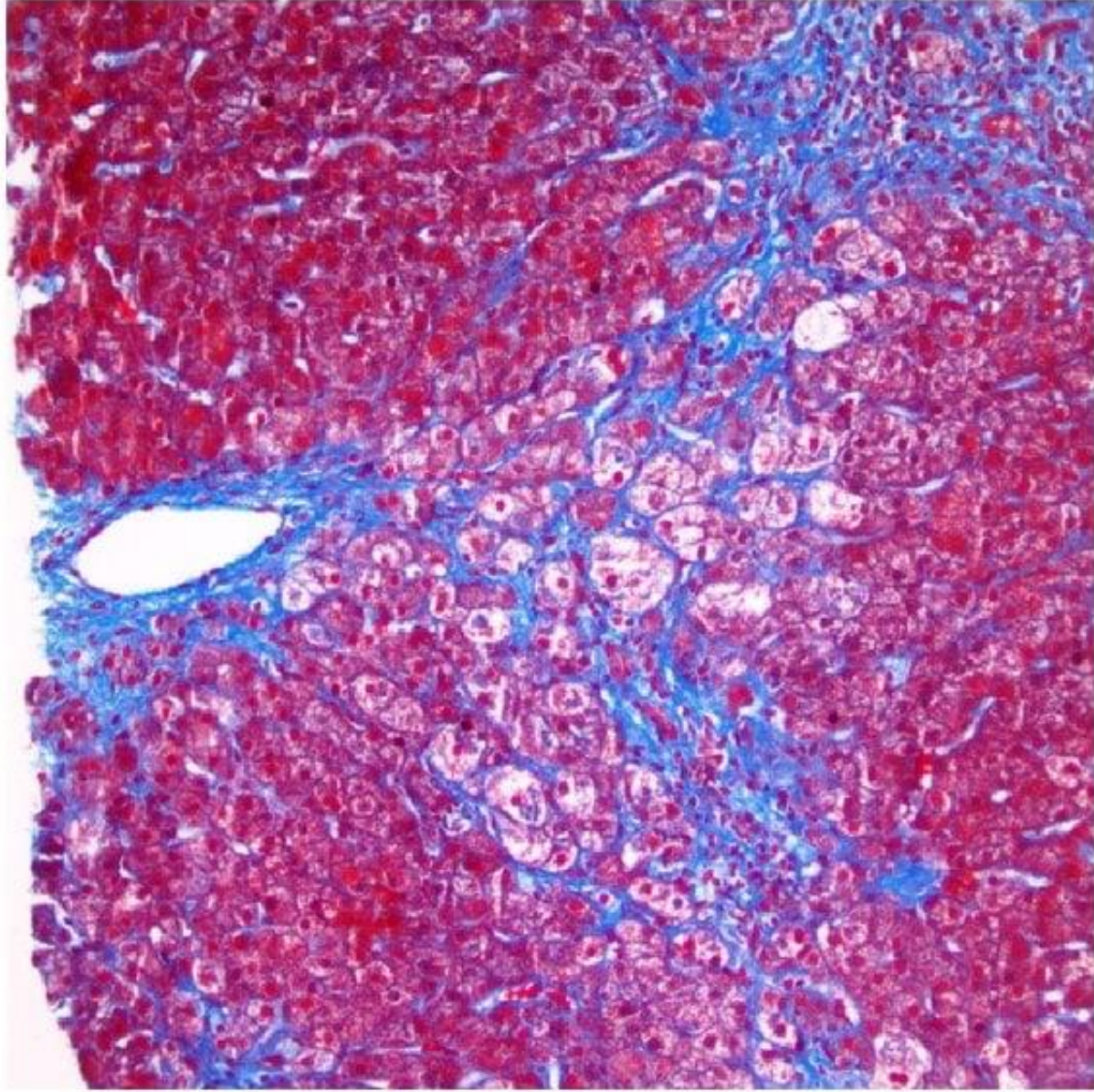
- **Lobular And Portal Inflammation:**

- Neutrophil
- Lymphomononuclear Cells

- **Fibrosis:**

- *+/-Chicken-wire* perisinusoidal fibrosis +/- zone III (centrilobular) fibrosis (early).
 - Late-stage disease - portal bridging.





- DDx of MASH:
- [Steatosis](#) - lacks ballooning degeneration and neutrophils.
- [Wilson disease](#).
- [Hepatitis C](#).
- [Drug-induced liver disease](#).

Pediatric NAFLD

- The main histological differences seen in some **pediatric NAFLD** when compared to adults has been the **distribution** of hepatocyte lipid droplets, inflammation and fibrosis location.

- In some pediatric patients with NAFLD, the lipid vacuoles are largest in the periportal hepatocytes and tend to decrease in diameter in pericentral area (zone 3).

- Similarly, inflammation and fibrosis is also seen around the portal tract (that is zone 1 predominance opposed to zone 3).
- When bridging fibrosis develops, the bridges connect portal to portal areas, leaving the central veins alone.

- However, these features are not specific for pediatric NAFLD and many cases have similar picture as that of adult NAFLD.

Brunt Grading System

Grade	Steatosis	Neutrophils	Ballooning	Chronic inflammation
1	$\leq 66\%$	scattered, rare	occasional or absent (zone 3)	none or mild acinar, none or mild portal
2	any amount ($>33\%$)	present	obvious ballooning	mild or moderate acinar, mild or moderate portal
3	panacinar, zone 3 predominant	present	present, obvious	mild acinar inflammation, mild or moderate (not marked) portal

Brunt Scoring

Score	Steatotic hepatocytes (%)	Foci of lobular lymphocytes	Ballooning hepatocytes
0	<5%	none	none
1	5-33%	<2	few
2	34%-66%	2-4	many
3	>66%	>4	(not assigned)

Staging steatohepatitis

Stage	Fibrosis	Notes
0	none	-
1	zone 3 perisinusoidal	may be focal or extensive
2	perisinusoidal and periportal	no bridging
3	bridging fibrosis	no nodule formation
4	nodule formation	-

Laboratory Tests

- The currently recommended screening test, ALT, is an inexpensive, universally available blood test.

- ALT is minimally invasive and has an acceptable sensitivity.
- The assay is standardized between facilities; however, the reporting of normal values is not.

- The cutoffs are 22 mg/dL for girls and 26 mg/dL for boys.
- A Canadian study found the upper limit of normal for ALT to be 30 mg/dL in children 1 to 12 years of age, and 24 mg/dL in those between 13 and 19 years.

- For the diagnosis of NAFLD, the use of 2 times the sex-specific ALT (ALT 50 for boys and 44 for girls) in overweight and obese children age 10 years or older has a sensitivity of 88% and a specificity of 26%.
- NASH is more common in children with ALT 80 U/L compared to those with ALT <80 U/L.

- Aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) have not been independently tested as screening tools for NAFLD in children.

- In the context of elevated ALT, higher AST and higher GGT are associated with worse histology.

- Elevated AST or GGT in the context of normal ALT may, however, represent a condition other than NAFLD.

بررسی بیوپسی های کبد با
تشخیص کبد چرب در آزمایشگاه
روشن آزما

حدود 600 بیوپسی کبد در آرشیو روشن آزما

• اطلاعات توسط همکار تحقیقاتی آزمایشگاه
روشن آزما (خانم پگاه پاکزادیان) استخراج
گردیده است.

- 20 مورد تغییر چربی کبد گزارش شده است.

- 13 مورد سن کم و بیشتر تغییر چربی از نوع میکرووزیکولر بوده و به بیماری های خاص متابولیک اشاره داشته است و یا ماکرو وزیکولر بوده ولی MASH نبوده است.

- هفت مورد به MASH می خورد در نتیجه آمار انجام بیوپسی در این بیماران حدود 7 به 600 است.

- از این تعداد 4 نفر پسر و 3 نفر دختر هستند.

Female / 12 Years Old

- Elevated Liver Enzymes Detected A Year Ago /
- Also Elevated Serum Lipids /
- Sonography: 1396.4.13: Fatty Liver Grade II /
- Muscle Cramps In Lower Extremities Since Five Years Ago, Mildly Elevated CPK Detected /
- Elevated Copper In 24 Hour Urine /
- R/O Wilson 'S Disease /
- Referral Case.

- **Liver Needle Biopsy:**

- - Liver With Micro And Macro Vesicular Fatty Change of Hepatocytes.
- - No Significant Portal Fibro Inflammatory Process.
- - See The Note.

- NB: Dear Colleague;
- Atomic Absorption Spectrophotometry Performed In Cancer Institute:
- Copper Level Was Normal (66.2 Microg / G).

Male / 11 Years Old

- Weight Gain A Year Ago: Weight: 46 Kg, Height: 139 Cm /
- Recent Weight (After Regiment): 42 Kg, Height: 142 Cm /
- Elevated Liver Enzymes Detected /
- Abdominal Sonography: Fatty Liver Grade 2 /
- Liver Needle Biopsy Performed And Paraffin Blocks Sent To Our Lab For Second Look.

- Liver Needle Biopsy:
- - Steatohepatitis.
- - Moderate Portal Fibrosis But Mild Portal Inflammatory Process.
- Brunt Score: Grade 2 /3 For Steatosis,
- Grade 1 / 3 For Steatohepatitis,
- Stage: 3 / 4.

Male / 7 Years Old

- Obesity Since Early In Life:
- Weight: 42 Kg, Height: 120 Cm /
- Elevated Liver Enzymes Detected In Two Years of Age /
- No Specific Workup And Treatment At That Time /
- Again Elevated Liver Enzymes Detected Eight Months Ago /
- Liver Sonography: 1397.8.20: Fatty Liver Grade I /
- R/O Wilson's Disease.

- Liver Needle Biopsy:
- -Liver With Mild Fatty Change (Only 10% Of Hepatocytes).
- - Mild Portal Fibro – Inflammatory Process.
- Brunt Score:
- Stage: 1 -2 / 4.
- Steatosis And Inflammatory Grade: 1 / 3

Female / 9.5 Years Old

- Diagnosis of Precocious Puberty Three Years Ago /
- Treatment With GnRh Agonists /
- Elevated Liver Enzymes Detected A Year Ago And Treatment Was Discontinued /
- Abdominal Sonography: 1397.4.20:
- Liver Span: 100 mm, Diffuse Increase In Parenchymal Echo of Liver: Fatty Liver Grade I /
- Weight: 41.800 Kg, Height: 137 Cm /
- Liver Needle Biopsy.
- Referral Case.

- Liver Needle Biopsy, Referral Case:
- - Liver With Mild Fatty Change (25% of Hepatocytes: Macro-Vesicular, 10%: Microvesicular Type).
- - No Significant Portal Fibro – Inflammatory Process.

Male / 10.5 Years of Age

- Obesity Since Early in Life /
- Weight: 51 kg, Height: 143 cm /
- Elevated Liver Enzymes Detected 4.5 Year Ago /
- Under Treatment With Diagnosis of Fatty Liver Since Then /
- Liver Needle Biopsy /
- Referral Case.

- Liver Needle Biopsy, Referral Case:
- Steato – Hepatitis.
- Brunt Score: Stage: 1 / 4. Grade: 1 / 3.

Female / 6.5 Years of Age

- Abdominal Pain Started Eight Months Ago /
- Mildly Elevated Liver Enzymes Detected /
- Weight: 29 Kg, Height: 120 cm /
- Liver Needle Biopsy Performed And Slides Sent to Our Lab.

- Liver Needle Biopsy, Referral Case:
 - - Mild Steatosis (Only 10% of Hepatocytes Show Macro – Vesicular Fatty Change).
 - - No Portal Fibro Inflammatory Process.
-
- NB: Dear Colleague:
 - Copper Content Was Checked By Atomic Absorption Spectrophotometry in Cancer Institute And Was Normal (70.4 Microgr / gr).

Male / 13 Years of Age

- Mildly Elevated Liver Enzymes Detected 15 Months Ago:
- Aspartate Aminotransferase (AST): 45 (10-40),
- Alanine Aminotransferase (ALT): 60 (10-40) /
- Abdominal Sonography Revealed Fatty Liver Grade 2 At That Time /
- Liver Gol And Vitamin E Since Then /

- Again More Elevation of Liver Enzymes Detected:
- 1404.1.29:
- Aspartate Aminotransferase (AST): 68 (10-40),
- Alanine Aminotransferase (ALT): 138 (10-40) /
- Liver Biopsy Performed Four Months Ago /
- Weight: 63 Kg, Height: 160 cm /
- Slides of Liver Sent to Our Laboratory.

- Diagnosis of Glycogen Storage Disease in Pathology
- Genetic Study Performed.

Specimen :

Liver biopsy

Clinical Data:

A 12 Y/O boy with elevated liver enzymes

Macroscopic :

A: Specimen labeled as liver biopsy and consists of a piece of needle-shaped tissue, measuring 0.4 cm in length and 0.2 cm in diameter (LEFT IN FORMALIN).

SOS: 1/1 E: 100%

B: Specimen labeled as liver biopsy and consists of a piece of needle-shaped creamy tissue, measuring 0.4 cm in length and 0.1 cm in diameter (LEFT IN ALCOHOL).

SOS: 1/1 E: 100%

Microscopic :

A&B: Sections show small sample hepatic parenchyma arranged in a lobular architecture with four portal tract. Hepatocytes exhibit prominent cytoplasmic changes characterized by homogenous, glassy, eosinophilic cytoplasm consistent with glycogen accumulation. Portal cells are diffusely present. Micro and macro steatosis is observed in scattered hepatocytes. The nuclei are centrally located and not displaced and no significant inflammatory or fibrosis is seen.

Diagnosis :

Liver needle biopsy:

- Metabolic liver disease suggestive of glycogen storage disease with moderate degree fatty changes
- No steatohepatitis is seen
- Stage of fibrosis can not be exactly diagnosed because of smallness of the sample

Patient ID:	PID3605-P	Physician:	Dr. Motamed
Patient Name:	Mahan Hakimi	Specimen Type:	Peripheral blood
Date of Birth:	1391	Reception Date:	1404/3/3
Gender:	Male	Report Date:	1404/4/8

Test Performed

Whole Exome Sequencing, Performed by MacroGen Inc., South Korea, NovaSeqX plus 150PE 8Gb 69SPL, Twist V2, 100X, Variant calling based on best practice of GATK. Genome ref version V. GRCh37.

Clinical Indications

The patient was born to a non-consanguineous marriage with elevated liver enzymes, hepatomegaly, spastic gait and is suspected of being affected by glycogen storage disease. There is a positive history of diabetes and MS in the family.

Table 1. Variants Relevant to Indication for Testing

Gene	Variant coordinates ^a	Associated disease/ Inheritance	Zygosity ^b	ACMG/ClinVar Classification ^c

^a (/): Exon_Intron_Num/Exon_Intron_Tot. In case of exonic variation the numbers are referring to the exon and in case of intronic, referring to intron.
^b **AD**=Autosomal Dominant; **AR**=Autosomal Recessive; **XL**=X-Linked; **XLR**=X-Linked Recessive; **DR**= Digenic Recessive
^c **Hom**=Homozygous; **Het**=Heterozygous; **Hem**=Hemizygous; **WT**=Wild Type
^c **VUS**=Variant of Uncertain Significance, **R**= Reported, **NR**= Not Reported

Table 2. Variants of Lower Significance/ Lower Clinical Correlation

Gene	Variant coordinates ^a	Associated disease/ Inheritance	Zygosity ^b	ACMG/ClinVar Classification ^c
<i>ABCB4</i>	Chr7 87092075 87092075 T C: NM_018849.3:(4/28): c.285A>G:p.Pro95Pro rs1281262436	Cholestasis, intrahepatic, of pregnancy, 3 614972 AD, AR Cholestasis, progressive familial intrahepatic 3 602347 AR Gallbladder disease 1 600803 AD, AR	Het	VUS/ NR
<i>GBE1</i>	Chr3 81691938 81691938 T C: NM_000158.4:(7/16): c.986A>G:p.Tyr329Cys rs80338671	Glycogen storage disease IV 232500 AR Polyglucosan body disease, adult form 263570 AR	<u>Het</u>	Likely Pathogenic/ Conflicting classifications of pathogenicity

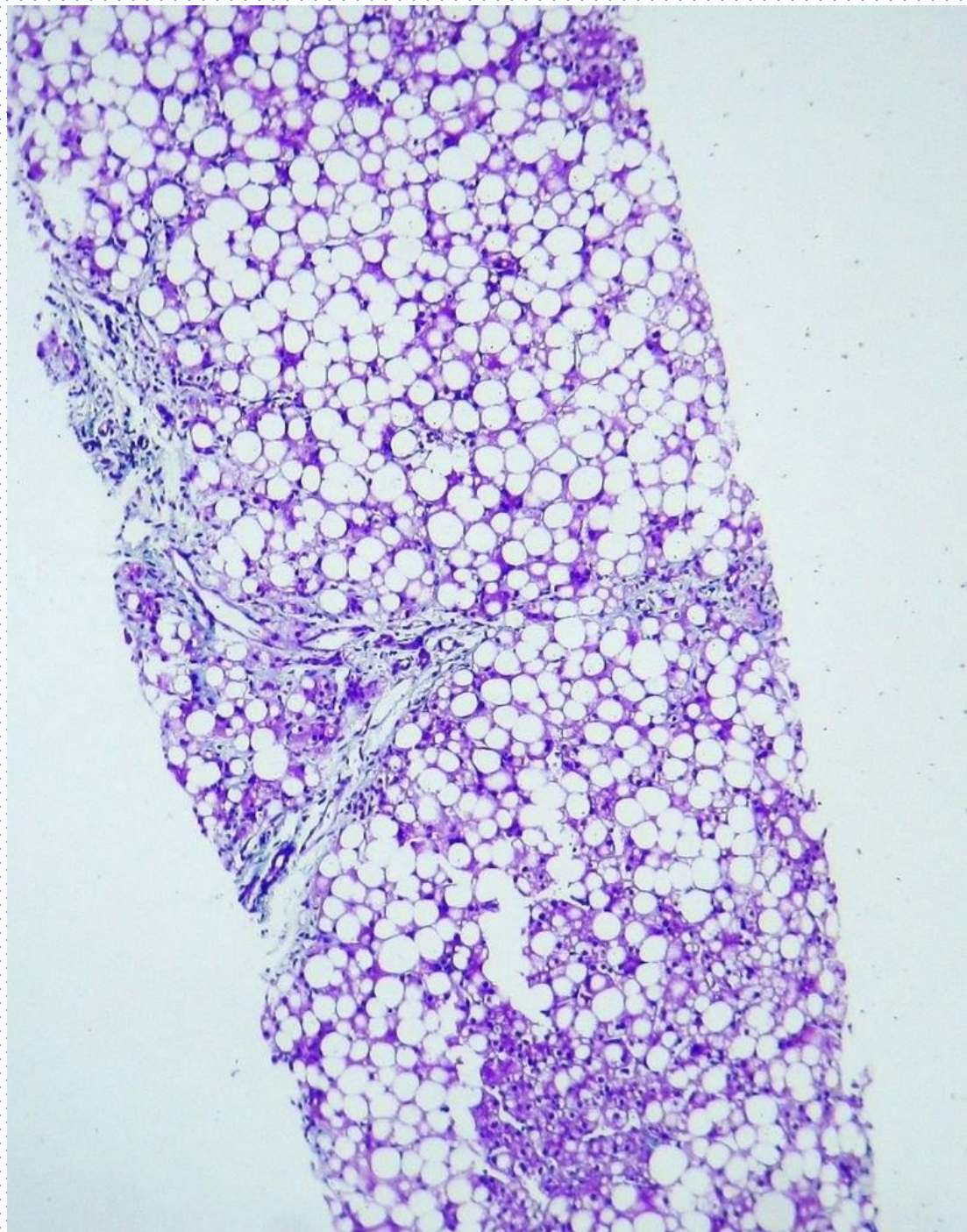
- Liver Needle Biopsy, Referral Case:
- - Liver With Predominantly Macrovesicular Fatty Change Involving 80% of Hepatocytes (Severe Steatosis).
- - Mild Portal Fibro - Inflammatory Process.

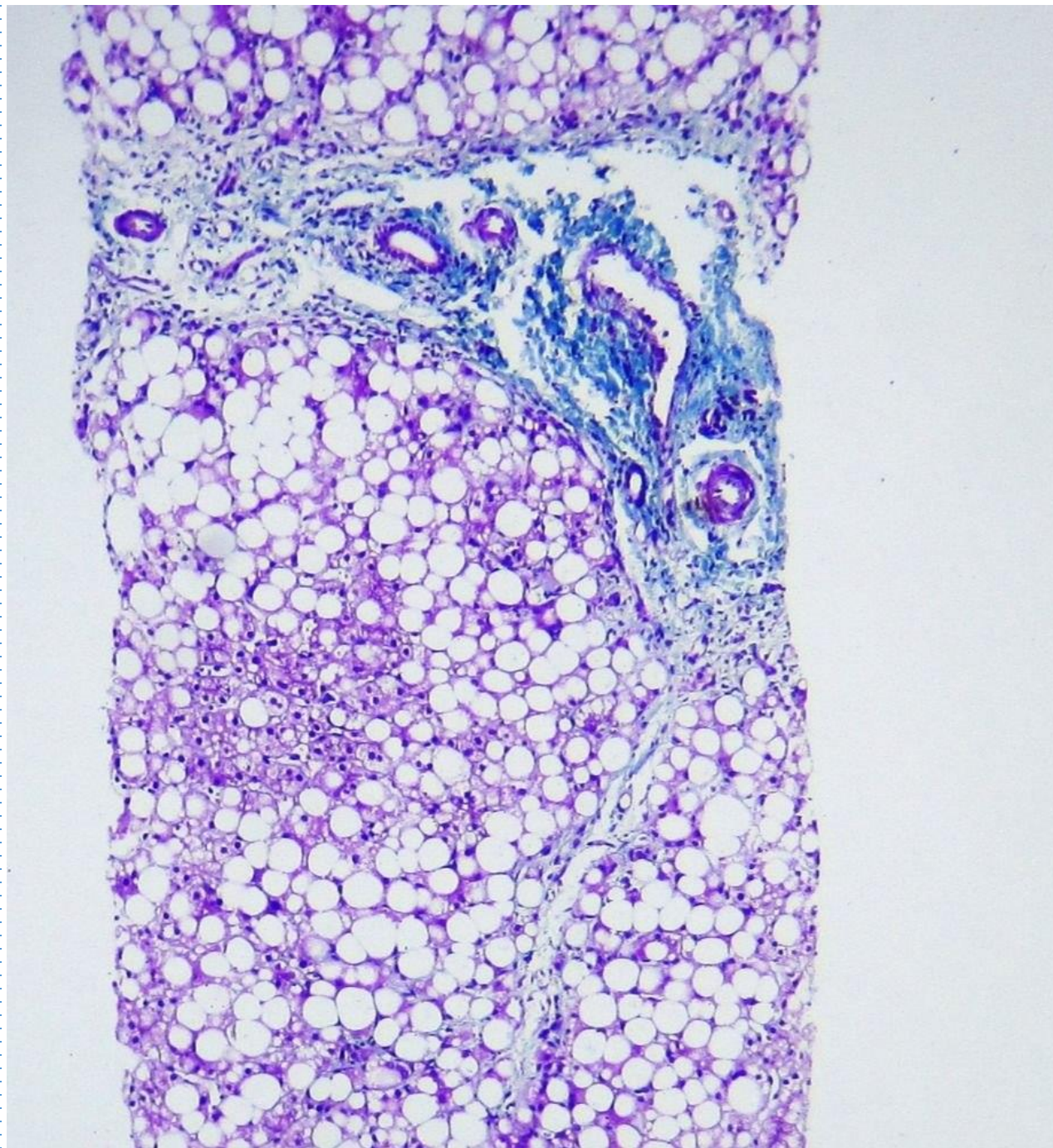
Other Causes of Fatty Change in Liver

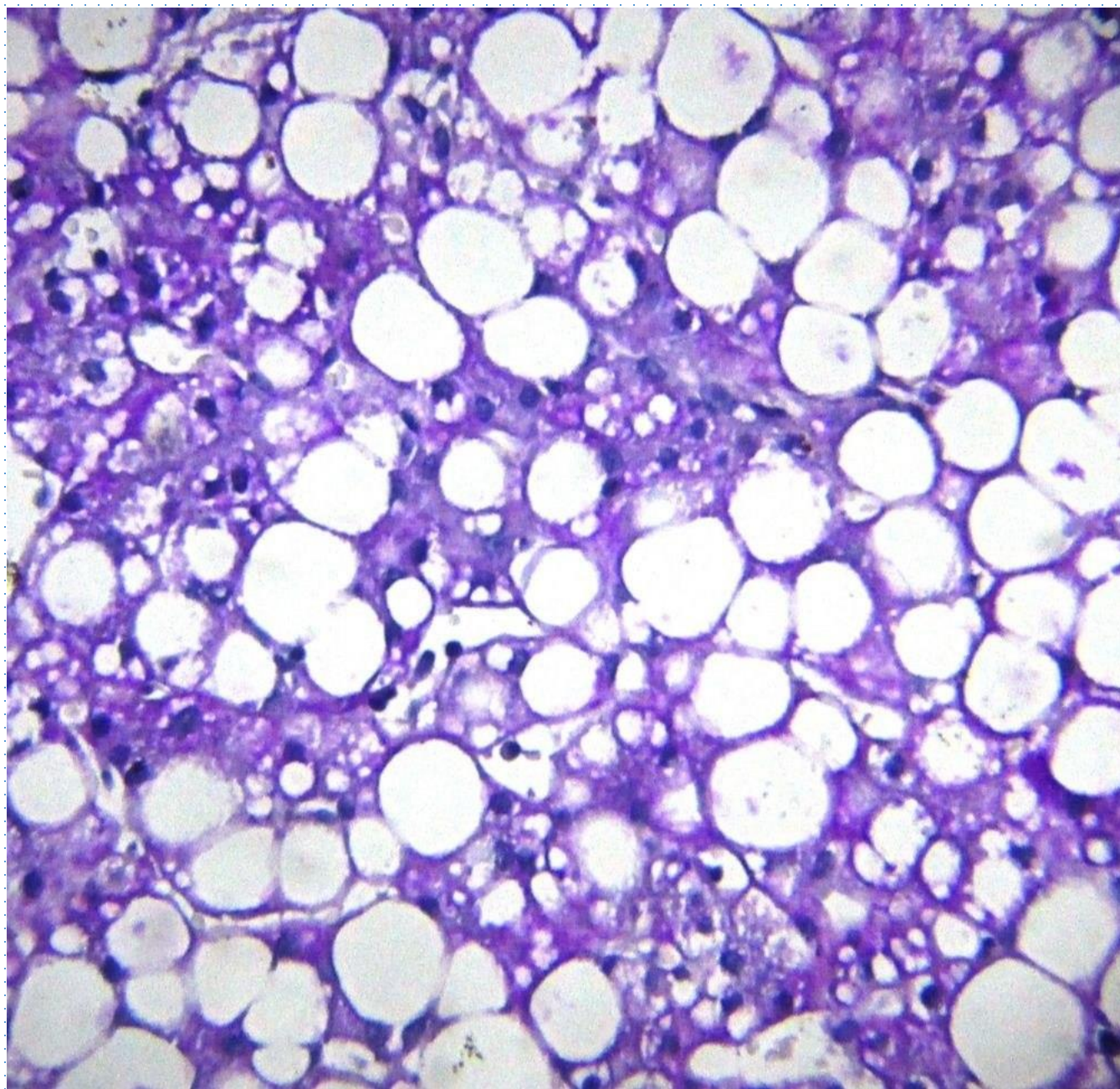
- [Fatty Change.mp4](#)

Male / 18 Months Old

- Preterm Birth (Eight Months, Born By Cesarean Section, Due To Oligohydramnios) /
- Low Blood Glucose Detected Early After Birth /
- Also Abdominal Distention Since Early In Life /
- Diarrhea Started In 13 Months Of Age /
- Hospitalized Two Months Later /
- Elevated Liver Enzymes And Fatty Liver In Sonography Detected /
- Patient Refuse To Eat Fruits And Sweet Stuff /
- Weight: 10 Kg, Height; 82 Cm /
- Liver Biopsy Performed And Paraffin Blocks And Slides Sent To Our Lab For Second Look.







- [483.pdf](#)

Male / 5.5 Years Old

- Abdominal Pain Started Two Years Ago /
- Abdominal Sonography: 1396.2.23:
- Mild To Moderate Fatty Liver /
- Mildly Elevated Liver Enzymes Detected /
- Also Hematuria Detected And Renal Micro-lithiasis Three Months Ago

- Parents Are Cousins /
- Another Sibling (8 Year Old Boy) Has Failure To Thrive And Low Blood Glucose Levels /
- Both Children Refuse To Eat Fruits And Sweet Stuff Since Early In Life /
- Referral Case.

- Liver Needle Biopsy:
- - Liver With Mild Fatty Change (Mainly Macrovesicular Type) (Near 30% of Hepatocytes).
- - No Significant Portal Fibrosis.
- - Minimal Portal Inflammatory Process.

- **Dear Colleague:**
- **Clinical History Is In Favor of Fructose Intolerance.**

Female / 20 Months

- Abdominal Distention Detected In Seven Months of Age /
- Abdominal Sonography Recently Revealed Hepatomegaly (Span: 178 mm),with Increased Homogenous Echogenecity /
- Also Elevated Liver Enzymes In Laboratory Tests /
- Liver Needle Biopsy.

- Liver Needle Biopsy:
 - - Liver With Severe Macro – Vesicular Fatty Change (95%).
 - - Progressing To Cirrhosis (HAI Score: Stage 5 – 6 / 6).
 - - No Significant Portal And Lobular Inflammatory Process Seen.

Male / 3 Months of Age

- Abdominal Distention Detected Early After Birth /
- Flu Like Symptoms Led to Hospitalization in Two Months of Age /
- Hepatomegaly Detected At That Time (Proved By Sonography) /
- Parents Are Cousins /
- Severely Elevated Triglyceride /
- Special Facies And Decreased Subcutaneous Fat Since Early in Life /
- Weight: 5.700 Kg, Height: 60 cm /
- Liver Needle Biopsy.

- A & B: Liver Needle Biopsy, Referral Case:
- - Severe Macro – Vesicular Fatty Change.
- - Portal – Portal Bridges (Moderate Portal Fibrosis)
 (HAI Score: Stage: 3-4 / 6).
- - No Significant Portal Inflammatory Process.

- NB: Dear Colleague;
- Facies And Absence of Subcutaneous Fatty Tissue is in Favor of Lipodystrophy Syndrome.

Male / 10.5 Years of Age

- Abdominal Pain Started A Year Ago /
- Mildly Elevated Liver Enzymes Detected Eleven Months Ago /
- Poor Growth Since Early in Life:
- Weight: 32 Kg, Height: 139 cm /
- Muscle Weakness Since Early in Life /
- Also Elevated Creatine Phosphokinase (CPK)Detected (701) (Normal: 24-195) /
- Parents Are Cousins /
- Liver Needle Biopsy Sent For Second Look.

- Liver Needle Biopsy, Referral Case:
 - - Marked Fatty Change, Mainly Micro – Vesicular Type.
 - - No Portal Fibro – Inflammatory Process.
- NB: Dear Colleague:
 - - Above Mentioned Changes, Clinical Findings (Mild Muscle Weakness) And Elevated CPK, Denotes Fatty Acid Oxidation Disorders.

- No Changes in Favor of Autoimmune Hepatitis Seen (Anti Smooth Muscle Antibody Was Reported as Positive in ----- Lab But Negative in ----- Lab And Anti Liver Kidney Microsomal Antibody Was Reported As Positive in ----- Lab But Negative in ---- Lab So It Appears To Be Technical Problems With These Tests).

