Beyond morphology: what radiologists should know about liver function tests

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LEARNING OBJETIVES

- To review the **main liver function tests (LFT)** with special focus on information relevant to radiology practice;
- To provide **imaging correlation with common patterns of liver function tests** abnormalities, illustrated by clinical examples from our practice.
- To explore ”tips and tricks” for radiologists related do **LFT.**

BACKGROUND

- Imaging techniques are widely used in the diagnosis of hepatic and biliary tract disorders.
- Despite major advances in hepatobiliary imaging, radiologists are frequently faced with **unspecific or unexpected imaging findings** for which a final diagnosis cannot be reached.
- **LFT are almost always available** and can provide valuable data to support a given diagnosis, therefore narrowing a list of differential diagnosis or avoiding imaging pitfalls.

LIVER FUNCTION TESTS

Excretory and detoxification function
Bilirubin
Seric Enzymes (hepatocellular injury/cholestasis)

Biosynthetic function
Albumin
Coagulation factors
Globulin

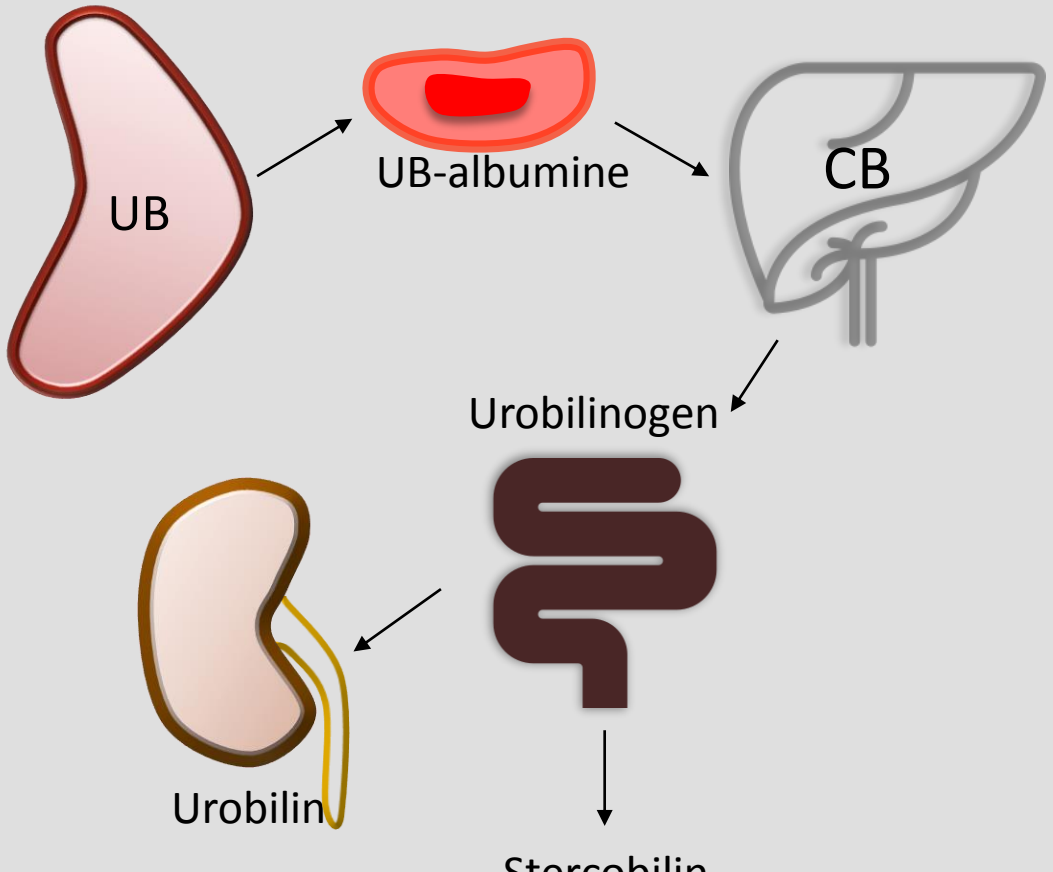
Other
Tumor markers
Tissue damage markers

1- Excretory and detoxification function : Bilirubin

- Bilirubin is the end product of heme degradation
- **70–90%** of bilirubin is derived from degradation of the hemoglobin of senescent red blood cells[1].

Unconjugated fraction (UB)
Insoluble in water
Bound to albumin

Conjugated fraction (CB)
Soluble in water
Intestinal excretion
(80%) and renal



Normal values
Total Plasmatic Bilirubin: **1-1.5** mg/dL
Conjugated fraction: **< 0.3** mg/dL

1- Excretory and detoxification function : Bilirubin

- ✓ ↑ UB is rarely due to liver disease – isolated elevation of UB is seen primarily in hemolytic disorders.
- ✓ Conjugated hyperbilirubinemia **almost always** implies liver or biliary tract disease.
- ✓ In most liver diseases, both CB and UB tend to be ↑ - fractionation of the bilirubin is **rarely helpful** in determining the cause of jaundice
- ✓ The presence of bilirubinuria **implies** the presence of liver disease – UB always binds to albumin in the serum and is not filtered by the kidney. Therefore, any bilirubin found in the urine is CB[1].

1- Excretory and detoxification function : Serum Enzymes

- No known function in the serum.
- The elevation of a given enzyme in the serum reflects its increased rate of entrance into serum from damaged liver cells.

1. **Hepatocellular damage:** Aminotransferases (AST and ALT).
2. **Cholestasis**: Alkaline phosphatase (AP) and γ-GT**.**

Normal values
Transaminases: **10-40 IU/L**
AP: **45-115 IU/L**
γ – GT: **9 - 48 U/L**

1 Aminotransferases (AMT)

- **Sensitive** indicators of liver cell injury and are most helpful in recognizing **acute** hepatocellular diseases;
- There is a **poor correlation** between the degree of liver cell damage and the level of AMT[1,2];
- Levels of up to **300 IU/L** are nonspecific and may be found in any type of liver disorder.

AST	Liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes
ALT	Found primarily in the **L**iver More **specific** indicator of liver injury than AST

2 Cholestasis enzymes

Alkaline Phosphatase (AP)

Non pathologic elevations	• > 60 years old (↑1-1.5 x) • Children/adolescent (bone AP) • Pregnancy (placental AP) • Individuals with blood types O and B after eating a fatty meal (intestinal AP)
< 3 x	• **Any type of liver disease**
> 4 x	• **Cholestatic liver disorders** • **Infiltrative liver diseases** (cancer, amyloidosis) • Bone conditions with rapid bone turnover (e.g.Paget's disease).

2 Cholestasis enzymes

AP

- The level of AP ↑ is **not helpful** in distinguishing between intrahepatic and extrahepatic cholestasis. There is **no difference** among the values found in obstructive jaundice due to cancer, common duct stone, Sclerosing Cholangitis, or bile duct stricture[1].

γ-GT:

- ↑ γ-GT is **less specific** for cholestasis than ↑ AP [2].
- Useful in the identification of the AP subtype (γ-GT is rarely elevated in conditions other than liver disease so if elevated with associated AP elevation, it will probably be due to the hepatic isoform of the AP).

2- Biosynthetic function : Albumin

- Synthesized exclusively by hepatocytes.
- Long half-life: **18–20 days** - **not a good indicator of acute or mild hepatic dysfunction[1]!**
- In hepatitis values **< 3 g/dL** should raise the suspicion of chronic hepatic disease [2].

Normal values
3.5-5.5 g/dL

Pitfalls:

- **Hypoalbuminemia** is not specific for hepatic disease:
  - **protein-losing enteropathies**
  - **nephrotic syndrome**
  - **chronic infections**
  - **malnutrition**

Should **not be** used for screening in patients in whom there is no suspicion of liver disease.

- **Ascites:** synthesis may be normal or ↑, but levels remain low because of the increased volume of distribution.

3- Other tests: Tumor markers

CT/MRI LI-RADS®

In lesions probably or definitely malignant but not specific of Hepatocellular carcinoma (HCC)[3] :

Alpha-fetoprotein (AFP): Normal: < 10 ng/ml

≥ 200 ng/mL→ high probability of **HCC**

≥ 100 ng/mL → moderate to high probability of **HCC**

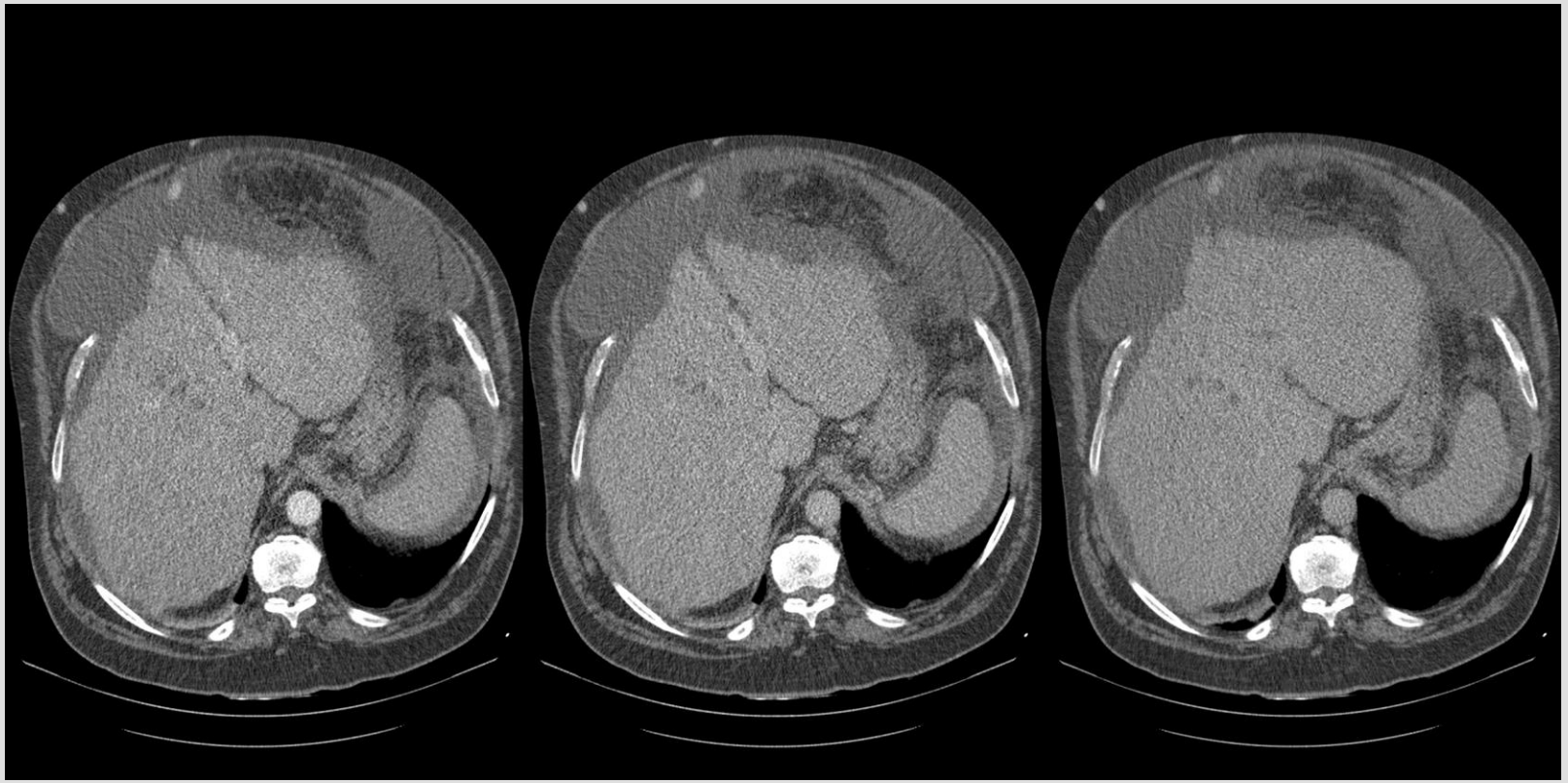
CA 19-9: Normal: ≤ 37 U/mL

≥ 200 U/mL→ high probability of **intrahepatic cholangiocarcinoma**

≥ 100 U/mL→ moderate to high probability of **intrahepatic cholangiocarcinoma**

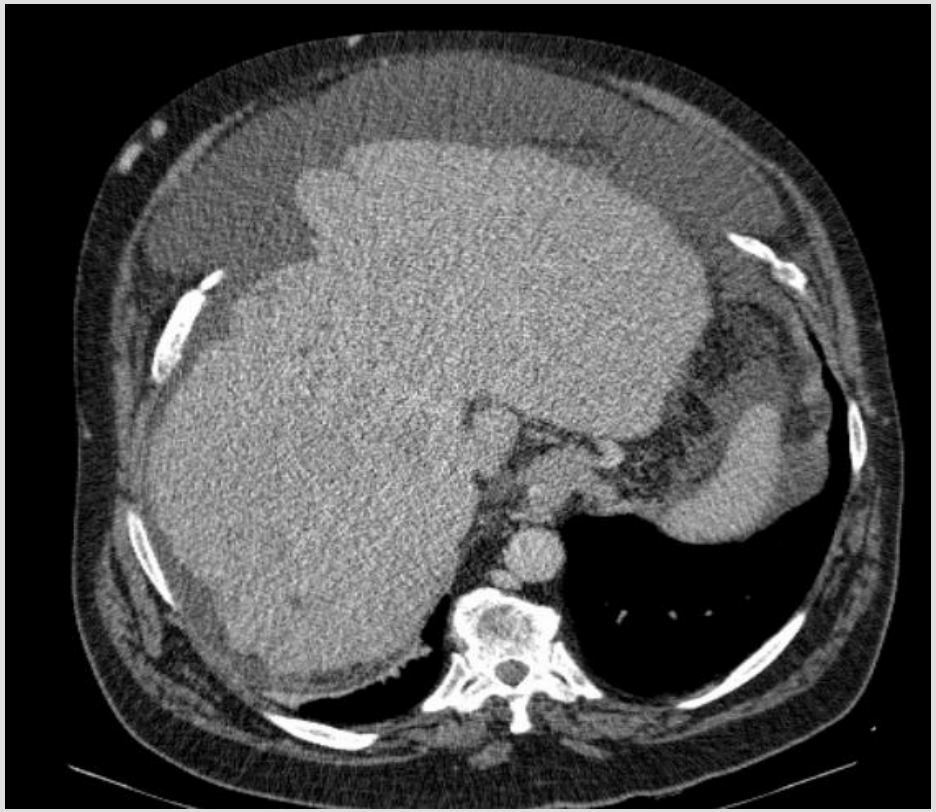
The trend over time is more helpful than a one-time value.

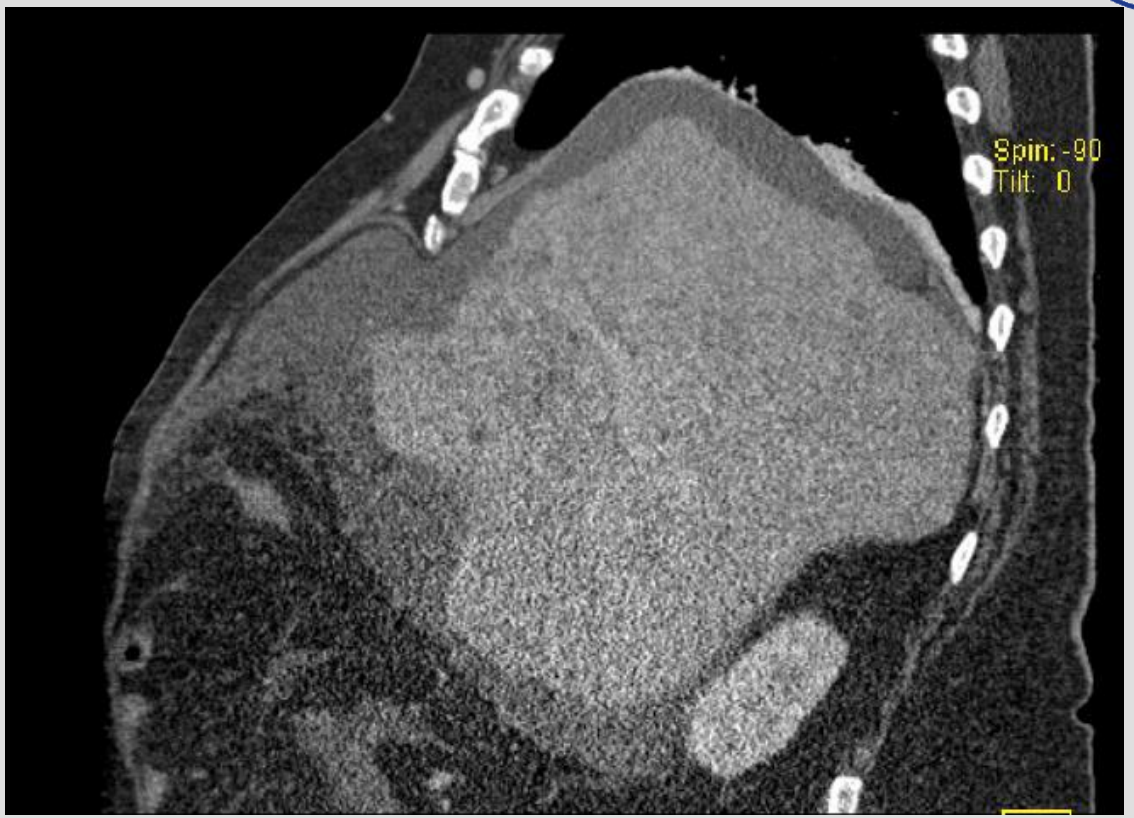
1 Clinical Case



57 Y, men, with moderate alcoholic intake, morbid obesity and previous normal LFT, presented to the emergency with an apparent new onset decompensated cirrhosis (ascites, jaundice and esophageal varices) and ↑ **AFP (232 ng/mL**) as well as bilirubinemia. **Abdominal CT** demonstrating liver with nodular contours and heterogeneous parenchyma, **without defined lesions**.

1 Clinical Case





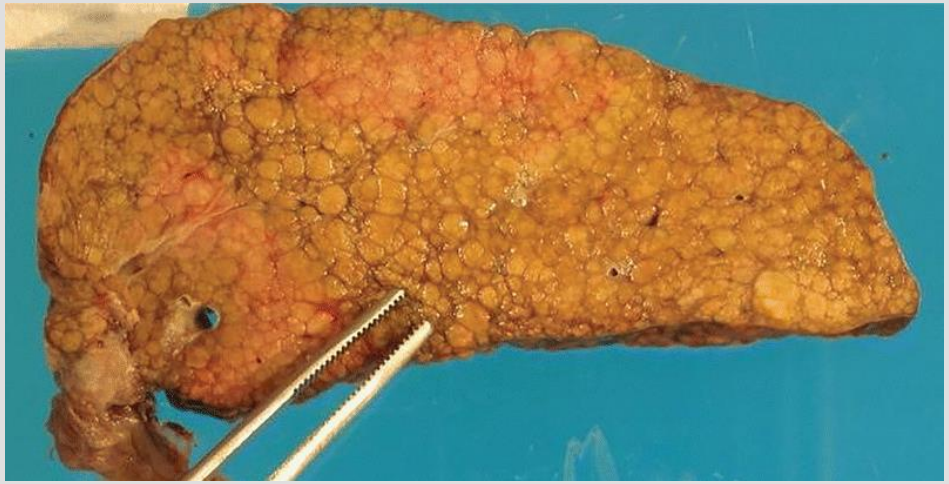
Interpreted as decompensated cirrhosis, the patient was admitted to stabilization and etiologic diagnosis. Progressive analytical and clinical deterioration. Hemocultures, urocultures, culture of the ascitic liquid, viral serology and auto-immunity tests were all negative. **Clinical suspicion due to ↑ AFP levels** prompted an hepatic trans jugular biopsy.

1

Clinical Case

Diffuse Cirrhosis-like Hepatocellular Carcinoma

- **Very rare variant of HCC**
- Presents as a multinodular liver without a dominant focal lesion
- Radiologically occult, often detected only in transplantation or autopsy [4].

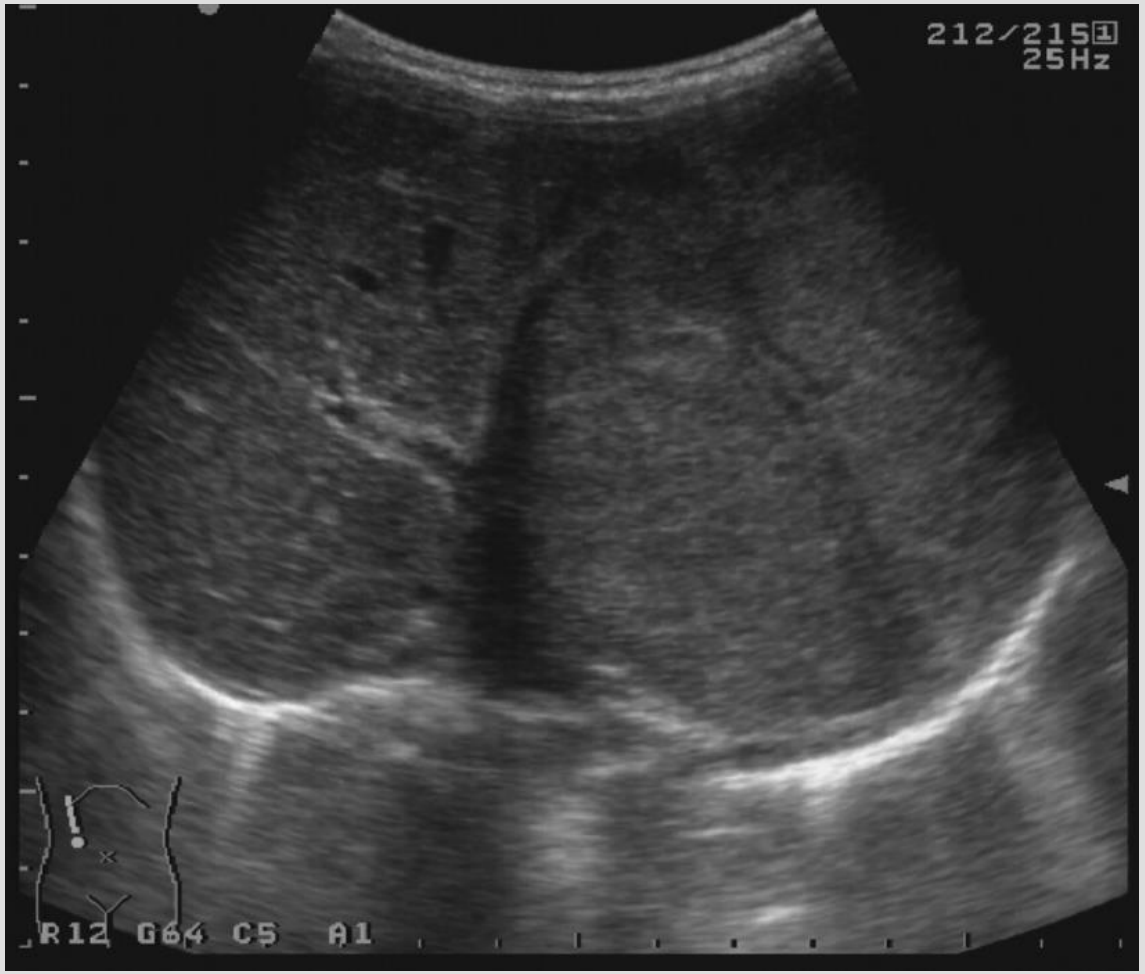


Diffuse cirrhosis-like HCC may be suspected when AFP is elevated and other etiologies of cirrhosis were excluded, but infiltrative forms of HCC may have normal AFP levels!

2 Clinical Case

1 month, **inadequate weight gain**

Abdominal US: solid **mass in the left lobe of the liver, well defined, heterogeneous,** with hypoechoic halo causing compression of the remaining left lobe.

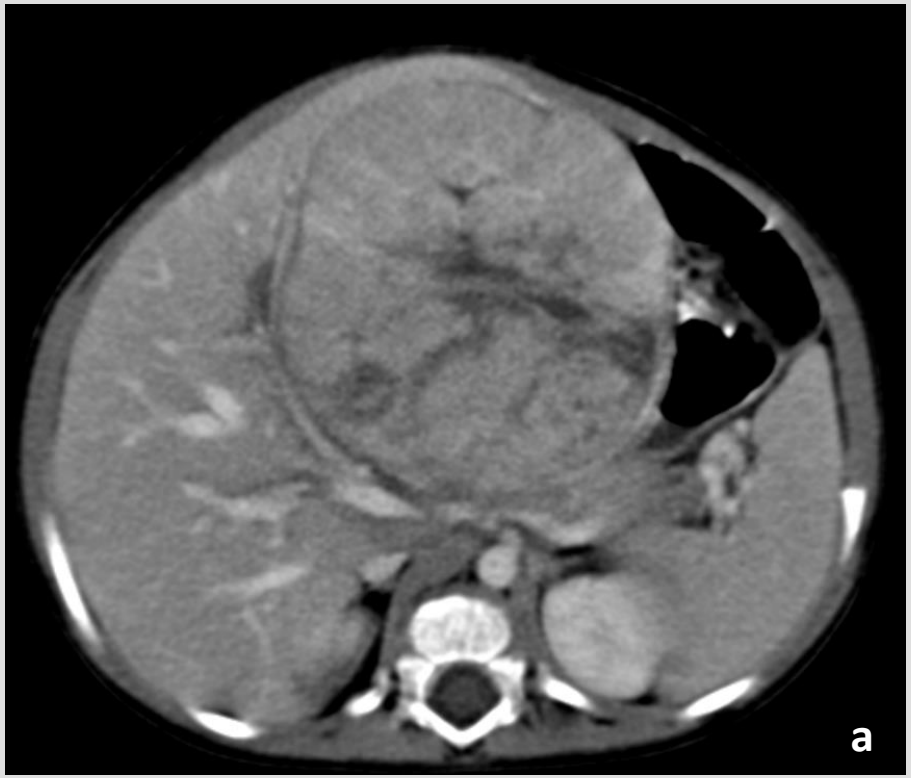


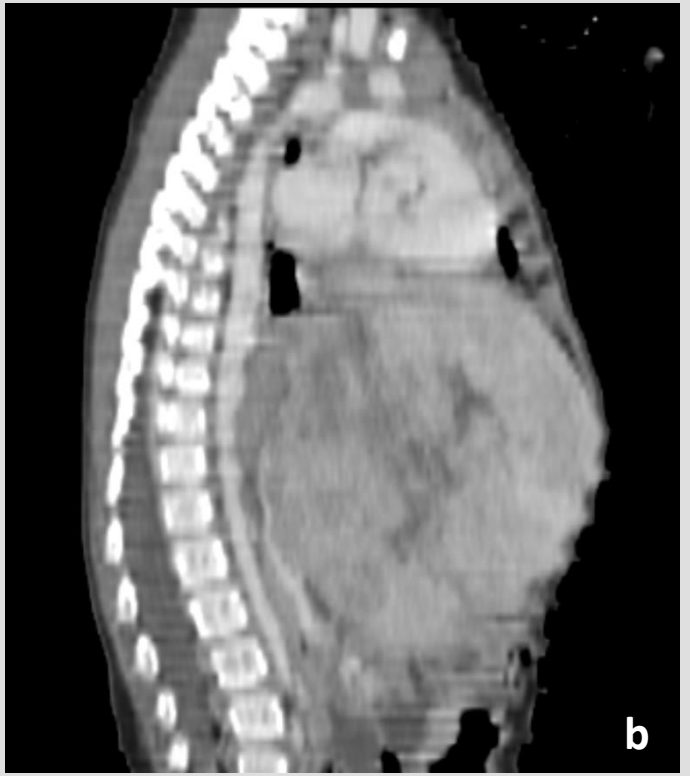
Pediatric liver masses

Age	Lesion	AFP	Liver disease
< 1 y	**Infantile Hemangioendothelioma**	Normal	✕
< 5 y	**Hepatoblastoma**	↑	✕
	Embryonal Rhabdomyosarcoma	Normal	✕
5-10 y	**Undifferentiated (Embryonal) Sarcoma**	Normal	✕
	Hamartoma	Normal	✕
>10 y	**Fibrolamellar Carcinoma**	Normal	✕
	Hepatocellular Carcinoma	↑	✓
	Epithelioid Hemangioendothelioma	Normal	✕
	Hepatocellular Adenoma	Normal	✕/✓
	Focal Nodular Hyperplasia	Normal	✕

Not all primary malignancies produce AFP (e.g fibrolamellar carcinoma), but the presence of elevated AFP levels **virtually excludes** a benign lesion! [5]

2 Clinical Case





Abdominal CT: **(a)** well defined heterogeneous mass with areas of necrosis. **(b)** Reduction of the caliber of the abdominal aorta below the celiac trunk by vascular redistribution to the liver due to the large hepatic mass. Imagiological findings were not specific. Age and **AFP positive** supported the diagnostic hypothesis of an **hepatoblastoma** that was then confirmed by histology.

AFP and age on pediatric liver masses differential diagnosis

3- Other tests: Tissue damage markers

Normal values
LDH: 115-211 g/dL

Lactate dehydrogenase (LDH):

Cytoplasmic enzyme present in several tissues: lower S and E for hepatic injury than AMT even with the hepatic isoform [2] .

Used to distinguish between **ischemic hepatitis** and viral hepatitis:

- Both with marked ↑ of AMT
- Sudden LDH ↑ in ischemic hepatitis (**20 to 250 x** within 1 to 3 days of hemodynamic damage)

3 Clinical Case

45 Y, women, submitted to orthotopic liver transplantation due to acute liver failure of toxic etiology.

Day 20 post-transplant:

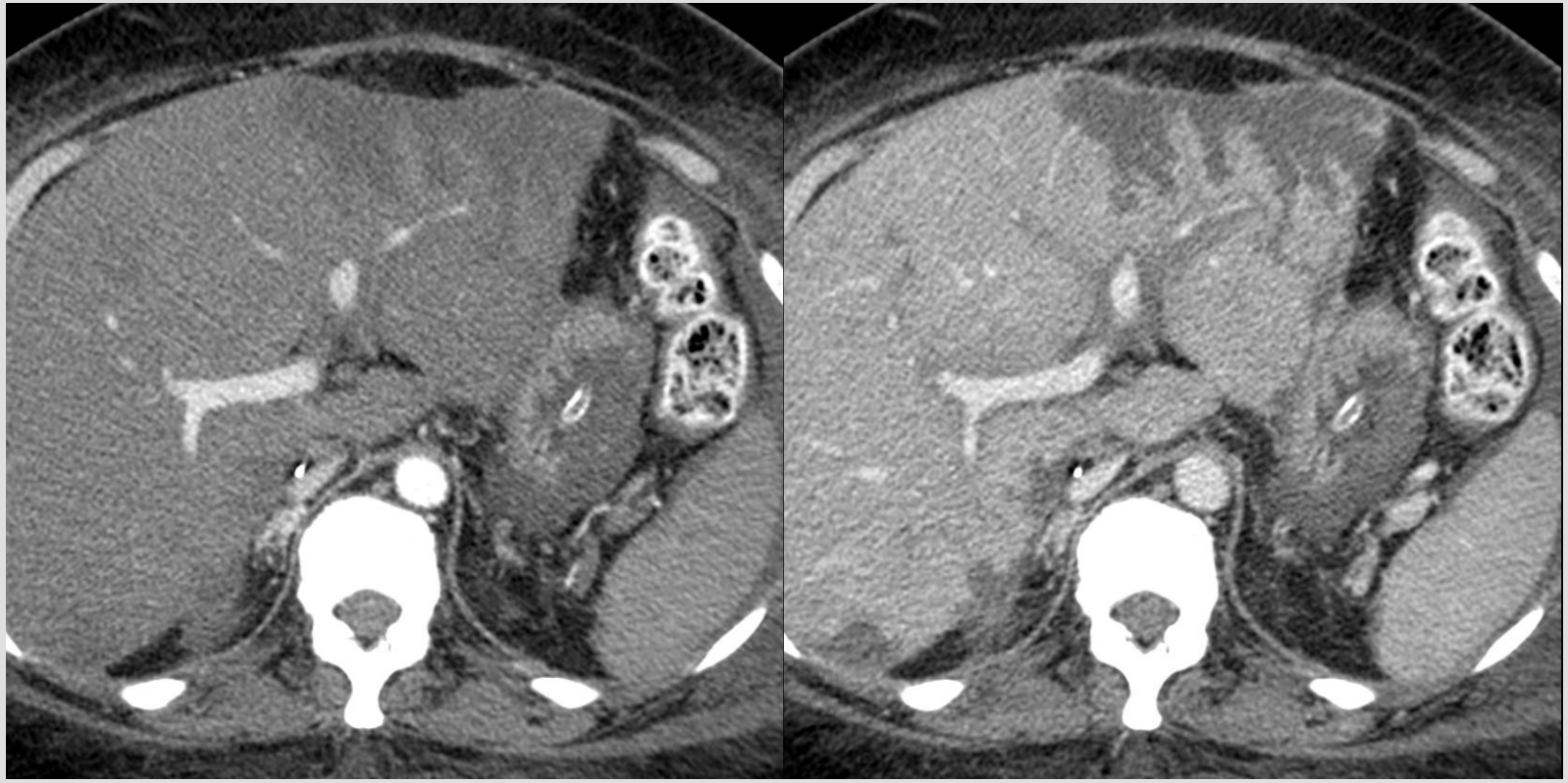
	D19	D20
AST	69	999
ALT	52	185
LDH	480	**2190**

Sudden, high ↑ (**20x**) of LDH and AMT

Abdominal US due to suspected ischemic complications:

- Limited examination (patches and edema of the subcutaneous cellular tissue). Liver with apparently homogeneous texture, permeable portal vein and branches. Hepatic artery (HA) not adequately assessed.
- Laboratorial exams **strongly suggested the existence of ischemic injury -** Abdominal Angio-CT was performed:

3 Clinical Case



Abdominal CT: Markedly heterogeneous texture, with multiple areas with **no evidence of enhancement** after contrast, in relation to **patchy hepatic necrosis**. Unidentified intrahepatic branches of the hepatic artery and absence of contrast in the hepatic artery, secondary to thrombosis (not shown).

Tissue damage marker (LDH) and AMT

STAGING OF CHRONIC LIVER DISEASE

1 Child-Pugh Score (5-15): estimates cirrhosis severity [6]

Factor	1	2	3
Albumin (g/dL)	> 3.5	3-3.5	<3.5
Bilirubin (mg/dL)	<2	2-3	>3
Ascites	---	controlled	poorly controlled
PT (↑sec)	<4	4-6	>6
Hepatic encephalopathy	---	minimal	advanced

Abdominal surgery peri-operative mortality

Class A: 5-6

Class B: 7-9

5% Compensated 10-15%

Class C: 10-15

Decompensated

STAGING OF CHRONIC LIVER DISEASE

2 MELD score: estimates prognosis of terminal liver disease and prioritize patients for transplant [7]

MELD	PELD (<12 YA)
Bilirubin	Bilirubin
INR	INR
Sodium	Albumin
Creatinine	Age
Dialysis (Y/N)	Growth failure (Y/N)

3 Mayo Score: predicts survival and need for transplantation in **primary sclerosing cholangitis**: [8]

Mayo Score
Bilirubin
AST
Age
Bleeding from varicose veins
Albumin

Patterns: Hepatocellular

Mild ↑ (AST:**ALT** < 1):

- **Nonalcoholic fatty liver disease**
- **Chronic Hepatitis B and C**

Others:

- Celiac disease
- α1AT deficiency
- Infiltrative liver disease.
- Drugs, hyperthyroidism, autoimmune liver disease.

Mild ↑ (**AST**:ALT >1):

- **Cirrhosis**
- **Alcoholic liver disease**

Others:

- Rhabdomyolysis
- Hemolysis
- Budd-Chiari syndrome
- Wilson's disease

Moderate to severe ↑ (ALT 5-15 x; AST >15x; **AST:**ALT>1**:**

- **Acute viral, ischemic and toxic hepatitis**
- **Acute phase of obstructive jaundice**;

Patterns: Cholestatic

Direct hyperbilirubinemia:

- **Lithiasic pancreatitis**
- **Acute cholecystitis**

→ ↑ AP, AST, ALT, total bilirubin

- **Chronic cholestasis**

→ ↑ AP; normal AST and ALT

↑ AP with normal bilirubin

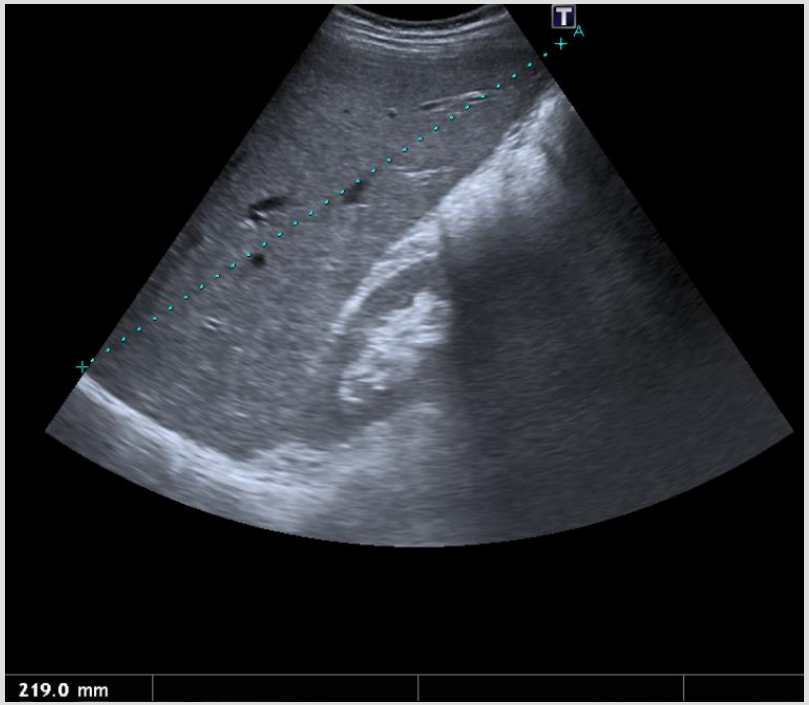
Look for **ductal anomalies** suggestive of CBP or CEP

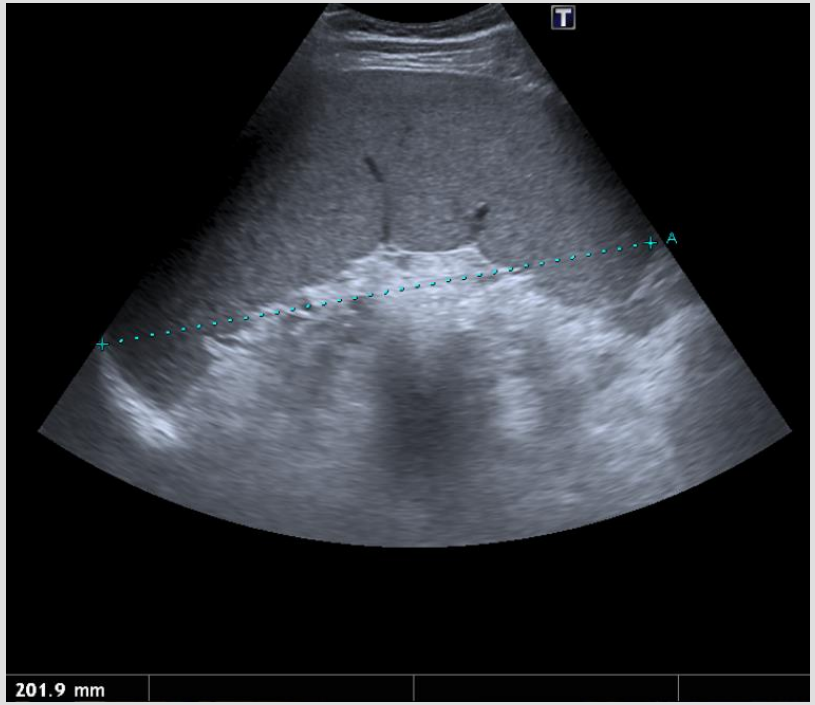
↑ AP with normal bilirubin and GGT

AP of non-hepatic origin: look for **Paget's disease** or **metastatic carcinoma of the prostate**

3 Clinical Case

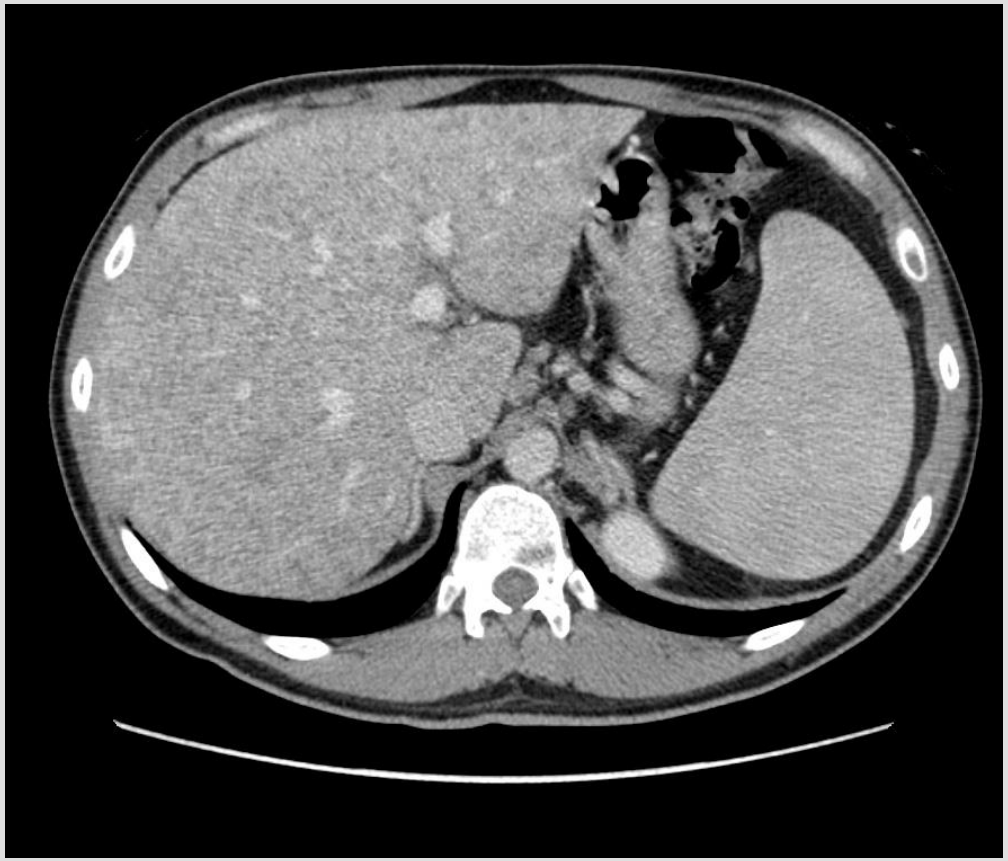
37 Y, women, presented to the emergency department with **fever** (37.5-38ºC), **headaches, myalgia and dyspnoea for a week**. No asthenia, anorexia or weight loss was reported. Physical examination with normal findings.

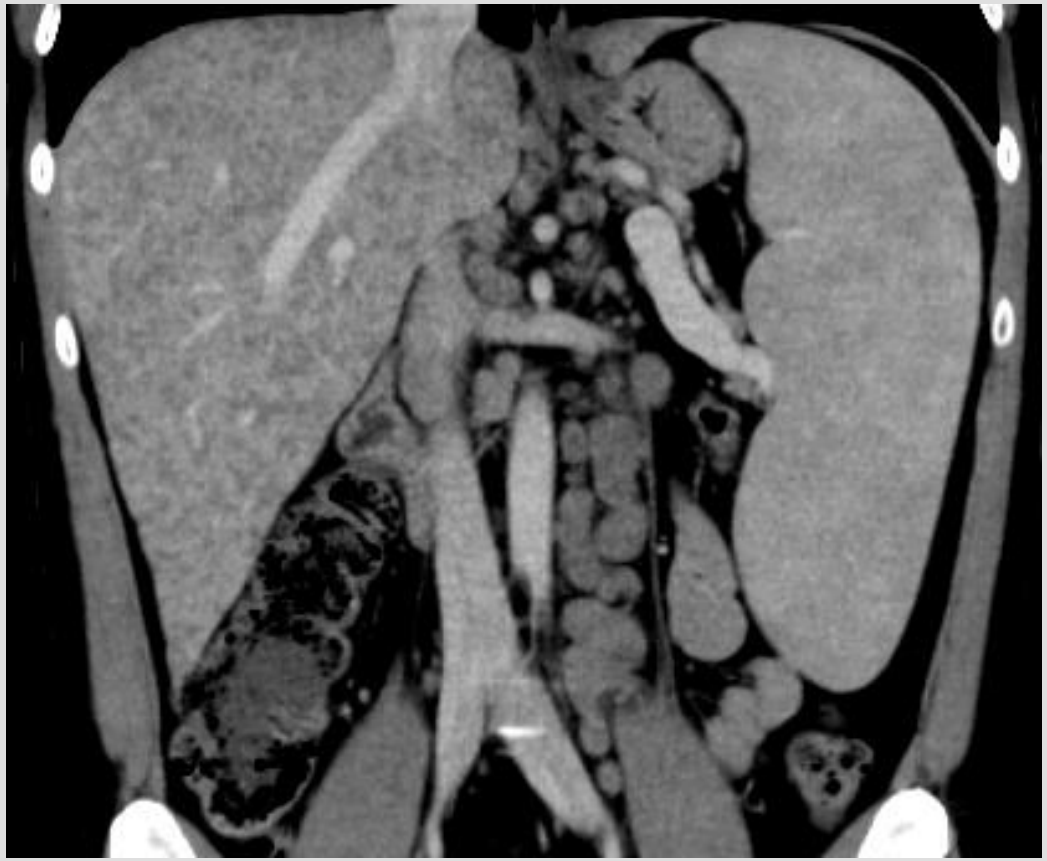




Abdominal US: **hepatomegaly** and **splenomegaly** with diffuse heterogeneous texture of both the liver and spleen.

3 Clinical Case





Admitted in the Infectious Diseases Department. **Thoraco-abdomino-pelvic CT:** presenting multiple liver and splenic **hypodense nodules** (5-20 mm). Also presented thoracic findings (hilar and mediastinal lymphadenopathies, interlobular septa thickening, pleural effusion and perilymphatic micronodulation with upper lobe predominance and confluent micronodules forming macronodules.

3 Clinical Case

Lymphoma	Sarcoidosis	Dissiminated Tuberculosis
▪ Hepatosplenomegaly ▪ Hepatic involvement (NHL: 15%; HL: 10%) – one nodule, multiple, diffuse infiltration	▪ Mild hepatosplenomegaly – homogeneous (++); hypodense nodules (5-20mm)	▪ Hepatosplenomegaly - hypodense nodules (5-20mm)
▪ Good general condition ▪ No constitutional symptoms	▪ Exuberant extra-pulmonary presentation	▪ Good general condition ▪ No constitutional symptoms ▪ Immunocompetent

3 Clinical Case

AST	**31 U/L**
ALT	**28 U/L**
LDH	**263 U/L**
AP	**387 U/L**
GGT	**293 U/L**
Total bilirubin	**0,8 mg/dL**

Sarcoidosis

- Hepatic impairment in 60%
- **AP and GGT** generally ↑**5-10x**. AMT with slight ↑ and less frequent.

The severity of alterations in liver funtion tests is related to the extent of granulomatous inflammation [9] .

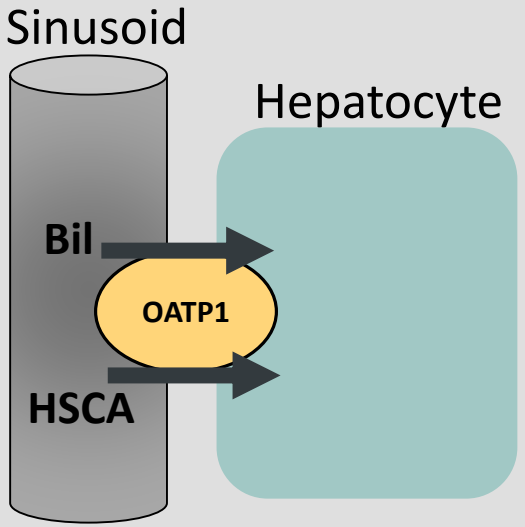
↑ AP and GGT with normal AMT

“Tips And Tricks”: Hepatospecific contrast and LFT [10]

- Gd-EOB-DTPA: hepato-specific contrast (HSCA) used in MRI.

- 50% biliary/ 50% renal excretion

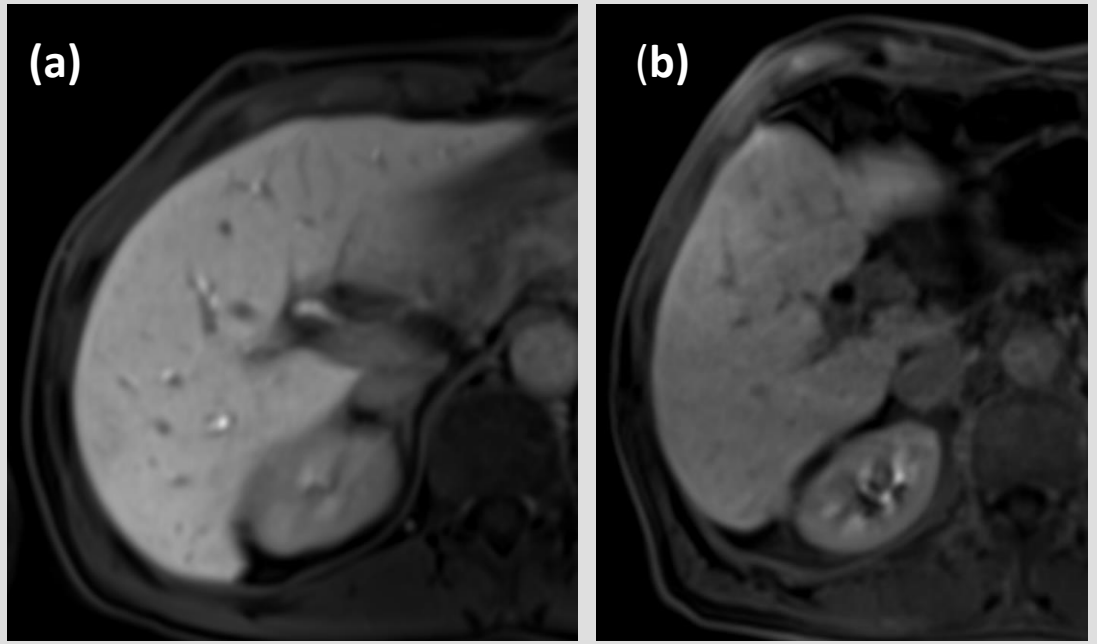
- Selective uptake by hepatocytes in the hepatobiliary phase (20 min) that allows a **greater enhancement of the parenchyma.**



- Contrast uptake to the hepatocyte is performed through **OATP1 transporter**
- In case of hepatic dysfunction with hyperbilirubinemia, there is less contrast uptake because the contrast

“Tips And Tricks”: Hepatospecific contrast and LFT [10]

Hepatobiliary phase enhancement is **less intense** in patients with hepatic impairment (Child-Pugh C).



Hepatobiliary phase images in Gd-EOB-DTPA-enhanced MRI of patients with Child-Pugh A **(a)** and C **(b).** Diffuse reduced hepatic enhancement as well as reduced biliary contrast excretion in image **b** due to the competition of Gd-EOB-DTPA with bilirubin for the same transporter.

Consider cost-effectiveness of the use of HSCA in patients with Child-Pugh C.

“Tips And Tricks”: Liver transplantation (LTx) complications[11]

Primary Graft Injury

Mild and moderate preservation injury
AMT peak within 48 h, followed by consistent decline. AP, GGT and bilirubin are typically slower to rise and fall (peak at days 7 to 14).

Primary Nonfunction:
AST>3000 within 7 days of LTx and INR >2.5, and/or acidosis : **highest priority for relisting for LTx**

Immune-mediated graft dysfunction (rejection)

Cholestasis occurs in acute and chronic rejection but chronic rejection tends to be more cholestatic.

Biochemical profile is not useful in predicting the presence or severity of rejection (histologic diagnose)

Biliary complications

Leaks: +++ first month after LTx. From asymptomatic to severe abdominal pain with ↑ bilirubin and other LFT abnormalities

Strictures: predominantly cholestatic profile.

Vascular

Hepatic artery and portal vein thrombosis: Profound elevation of AMT in the early postoperative period.

“TAKE HOME” MESSAGES

- ✓If altered LFT: understand the pattern of injury (hepatocellular / cholestatic /mixed) and the AST / ALT ratio in order to help with differential diagnosis.
- ✓Integrate Child-Pugh score in the decision to use hepato-specific contrast.
- ✓Be familiar with staging scores so that the radiologist can have **an active role** in multidisciplinary meetings.
- ✓In pediatric liver masses, elevation of AFP virtually excludes the presence of a benign lesion.
- ✓In the study of transplant patients, marked increases in AMT and LDH strongly indicate the possibility of ischemic complications and should prompt investigation.

CONCLUSION

An understanding of imaging findings associated with common patterns of liver enzyme abnormalities allows the integration of radiology, clinical, and laboratory data to arrive at a more informed and comprehensive diagnosis.

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