Le epatiti autoimmuni : Una patologia in aumento?

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Diagnosis and management of autoimmune hepatitis

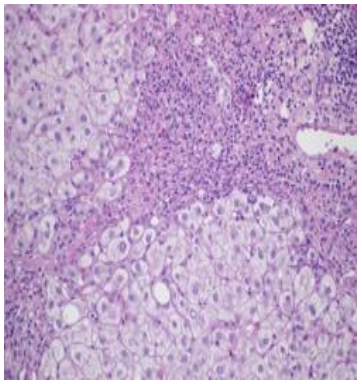
Luigi Muratori,[1,3] Ansgar W Lohse,[2,3] Marco Lenzi[1,3]

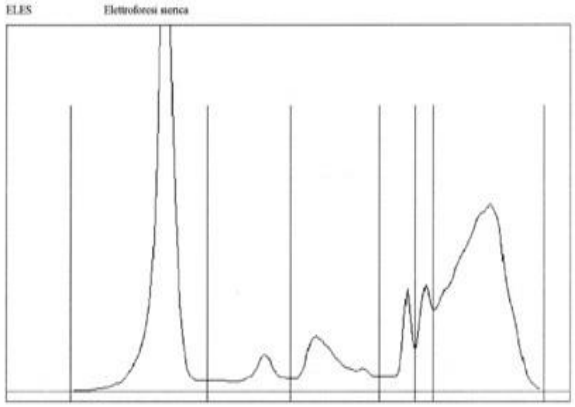
Autoimmune hepatitis is an inflammatory disease of the liver of unknown cause that may progress to liver cirrhosis and end stage liver failure if diagnosis is overlooked and treatment delayed. The clinical presentation is often that of acute hepatitis, sometimes very severe; less frequently, it can be insidious or completely asymptomatic. The disease can affect people of any age and is more common in women; its incidence and prevalence seem to be on the rise worldwide. An abnormal immune response targeting liver autoantigens and inducing persistent and self-perpetuating liver inflammation is the pathogenic mechanism of the disease. A specific set of autoantibodies, increased IgG concentrations, and histological demonstration of interface hepatitis and periportal necrosis are the diagnostic hallmarks of autoimmune hepatitis. Prompt response to treatment with corticosteroids and other immunomodulatory drugs is almost universal and supports the diagnosis. The aims of treatment are to induce and maintain long term remission of liver inflammation. Treatment can often even reverse liver fibrosis, thus preventing progression to advanced cirrhosis and its complications. Most patients need lifelong maintenance therapy, and repeated follow-up in experienced hands improves the quality of care and quality of life for affected patients.

BMJ 2023

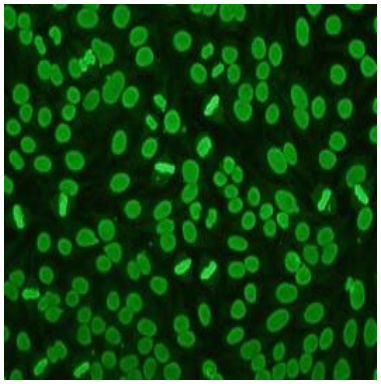
Autoimmune Hepatitis: an unresolving inflammation of the liver of unknown cause

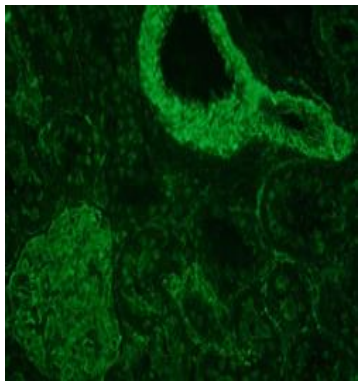
1. interface hepatitis 2. hypergammaglobulinemia

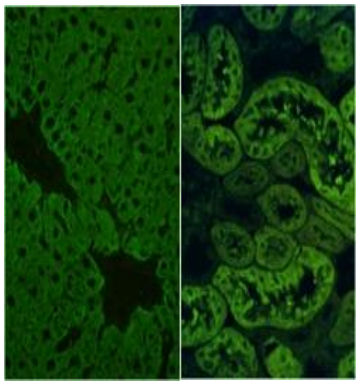




3. non organ-specific autoantibodies







Diagnosis and management of autoimmune hepatitis

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Autoimmune hepatitis can affect all ages and all populations, regardless of race and ethnicity.[16] The pooled worldwide annual incidence and prevalence are 1.37 and 17.44 per 100 000 people, respectively. Pooled annual incidences for Asian, European, and American populations are 1.31, 1.37, and 1.00 per 100 000. Pooled prevalences for Asian, European, and American populations are 12.99, 19.44, and 22.80 per 100 000, respectively.[17] The lower prevalence in Asian in comparison with European and American populations can be explained by the different genetic background, as European and North American people are mainly white, with a higher frequency of HLA DR3 and DR4 in patients with autoimmune hepatitis. In addition, environmental factors such as better living conditions, changes in lifestyle habits, and diet remodulate the intestinal microbiome, which in turn affects the immune system and the gut-liver axis.[18]

In keeping with the increasing rate of autoimmune phenomena,[19] autoimmune hepatitis seems to be on the rise according to population based studies conducted in Denmark, where incidence increased from 1.37 in 1994 to 2.33 in 2014,[20] and in England, where the incidence doubled from 1.27 to 2.56 during the 1997-2015 period.[21] In addition, a more northerly latitude is associated with an increased incidence of autoimmune hepatitis in the UK, possibly owing to lower sun exposure and the consequent lack of vitamin D.[22]

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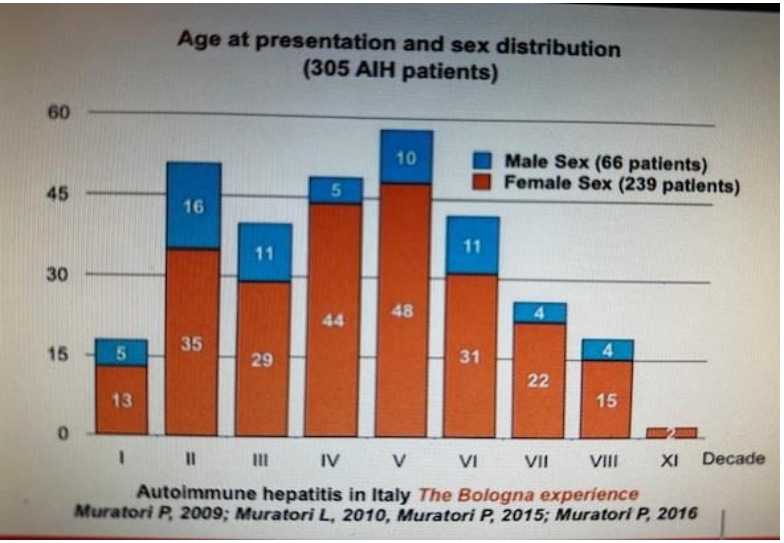

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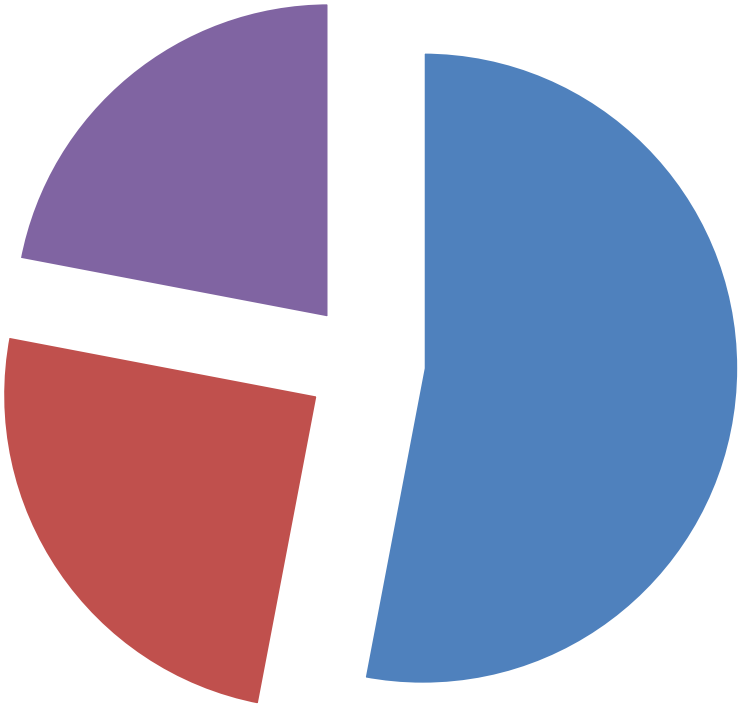
Presentation of disease at onset

- Broad range from asymptomatic to acute/severe or even fulminant

ASYMPTOMATIC ONSET
(about 22%) Abnormal liver blood tests

ACUTE ONSET (about 25%)
- acute exacerbation of chronic AIH
- true acute AIH without histological findings of chronic liver disease

Autoantibodies or other classical features can be absent (SAIH); not always responsiveness to corticosteroids

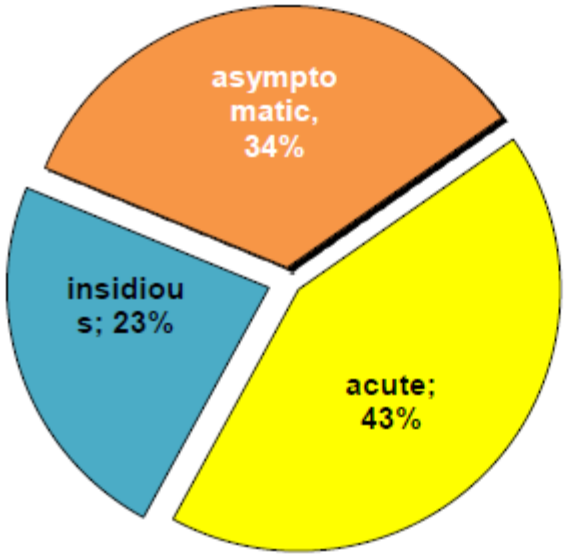


INSIDIOUS ONSET
(about 53%)
fatigue, general ill health, right upper quadrant pain, lethargy, malaise, anorexia, weight loss, nausea, pruritus, fluctuating jaundice and polyarthralgia involving the small joints without arthritis, sometimes dating back years

One third of patients at diagnosis have already developed cirrhosis

Clinical presentation of AIH

The Bologna experience - 2018 update



Acute onset	median	range
ALT (X unl)	25	1.3-88
bilirubin (mg/dl)	9	0.3-49
gammaglob (g/l)	24	10.5-60

prolonged INR: 64%

bilirubin > 7 mg/dl: 60%

γ-glob > 15 g/l: 80%

Fulminant presentation of autoimmune hepatitis: clinical features and early predictors of corticosteroid treatment failure

Manuel Mendizabal[a], Sebastián Marciano[c], María G. Videla[d], Margarita Anders[e], Alina Zerega[f], Domingo C. Balderramo[g], Matías R. Tisi Baña[b], Martín Barrabino[g], Octavio Gil[f], Ricardo Mastai[e], Silvina Yantorno[d], Adrián Gadano[c] and Marcelo O. Silva[a]

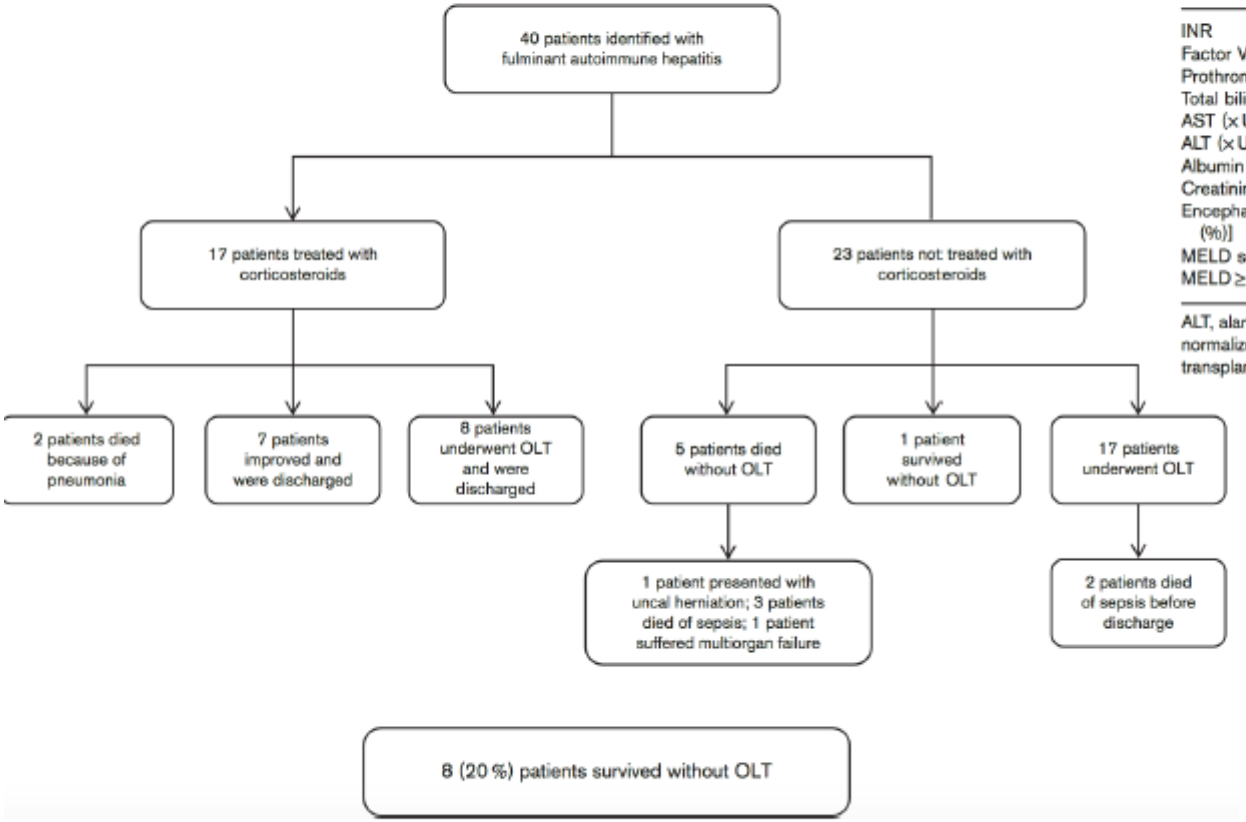


Table 3. Factors associated with steroid failure at initiation of therapy

Variables	Alive ($n=7$)	Death or OLT ($n=10$)	P
INR	1.9±0.4	3.7±2.1	0.02
Factor V (%)	53±14	31±12	0.007
Prothrombin time (%)	42±9	23±11	0.002
Total bilirubin (mg/dl)	16.6±11.6	22.6±8.3	0.2
AST (×ULN)	24±23	24±14	0.9
ALT (×ULN)	17±15	19±13	0.7
Albumin (mg/dl)	2.6±0.7	2.8±0.3	0.4
Creatinine (mg/dl)	0.6±0.1	0.8±0.3	0.2
Encephalopathy grade ≥3 [*n* (%)]	0 (0)	7 (70)	0.01
MELD score	23±4	31±7	0.008
MELD ≥27 [*n* (%)]	1 (14)	8 (80)	0.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; ULN, upper limit of normal.

European Journal of Gastroenterology & Hepatology 2015, 27:644-648

Antibody	Target Antigen	Liver Disease
ANA	Chromatin, ribonucleoproteins, ribonucleoprotein complexes	**Type1 AIH**,PBC,PSC, Drug-induced, Chronic hepatitis B&C,NAFLD
SMA	Microfilaments(filamentous actin) & intermediate filaments (vimentin,desmin)	**Type1 AIH**,PBC,PSC, Drug-induced,Chronic hepatitis B&C,NAFLD
LKM 1	Cytochrome P450 2D6 (CYP2D6)	**Type 2 AIH** Chronic hepatitis C
LC 1	Formiminotransferase cyclo deaminase (FTCD)	**Type 2 AIH** Chronic hepatitis C
pANCA (atypical)	Nuclear lamina proteins	Type1 AIH PSC
SLA	tRNP(SER)Sec	AIH,Chronic hepatitis C

	ANA	SMA	SLA
Pooled sensitivity	0,65	0,59	0,19
Specificity	0,75	0,93	0.99

Subclassification

- AIH-Type 1

- almost for 90% of AIH cases
- detection of ANA, SMA or anti-SLA/LP
- association with HLA DR3, DR4 and DR13
- any age
- variable clinical and histopathological severity;
- rare failure of treatment but variable relapse rates after drug withdrawal and variable need for long-term maintenance therapy

AIH- Type 2

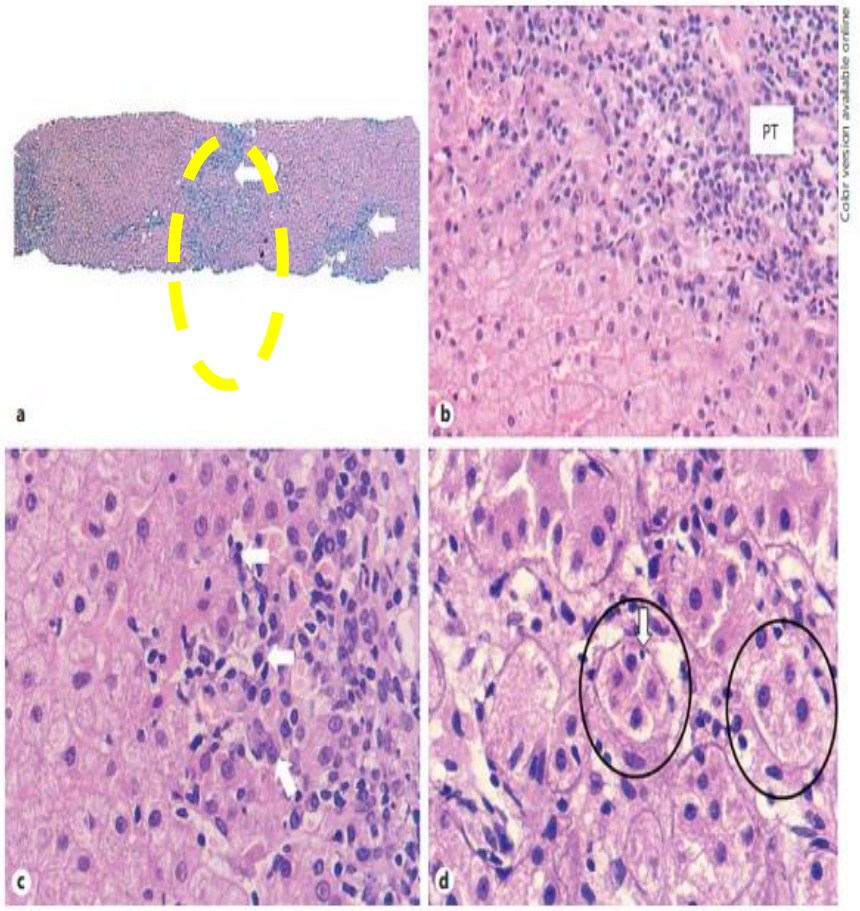
- for up to 10% of AIH cases
- detection of anti-LKM1, anti-LC1 and rarely antiLKM3
- association with HLA DR3 and DR7
- in childhood and young adulthood
- clinical and histopathological severity commonly acute and advanced
- frequent failure of treatment and frequent relapse rates after drug withdrawal; need for long-term maintenance

Histology

Guideline statements*	
Histological demonstration of hepatitis is a prerequisite for the diagnosis of AIH and needs to be part of the initial diagnostic work-up	II-2
No morphological features are pathognomonic of AIH. **Suggestive of AIH: interface hepatitis, periportal necrosis, emperipolesis and rosetting of hepatocytes. These features should be reported by the pathologist in addition to grading (hepatitis activity index) and staging of disease**	II-2
Pericentral necrosis may be present in the acute onset of AIH and histologically indistinguishable from DILI	II-3
The simplified scoring system (2008) of the IAIHG is a useful clinical tool. By considering response to treatment, the revised scoring system (1999) of the IAIHG can be helpful in diagnosing difficult cases	II-2
Coexistence of features of AIH and cholestatic liver diseases can be observed, both at diagnosis and during follow-up. Diagnostic tests for PBC and PSC should be performed in patients showing features of cholestasis	II-2
In adult patients with AIH and cholestatic lab changes, and in all children with AIH, (MR)cholangiography should be performed in order to recognize sclerosing cholangitis	II-3

*Statement numbers: 15–20
EASL CPG AIH. J Hepatol 2015;63:971–1004

Histology



TYPICAL HISTOLOGYCAL FEATURES

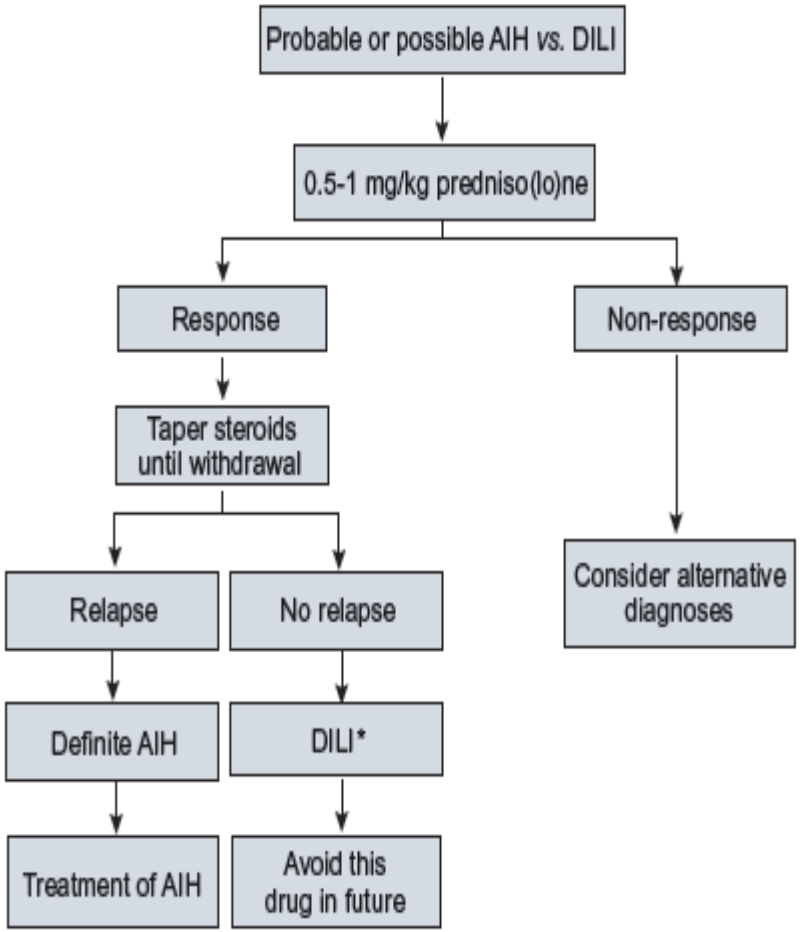
a) Chronic hepatitis pattern with **mononuclear cell inflammatory infiltrate** in PT
b) <u>Interface hepatitis</u>: portal lymphoplasmacytic infiltrate extending into the lobule
c) Higher magnification shows many **plasma cells** at the portal-parenchymal interface
d) Hepatocellular **<u>rosette</u>** formation and **<u>emperipolesis</u>**

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

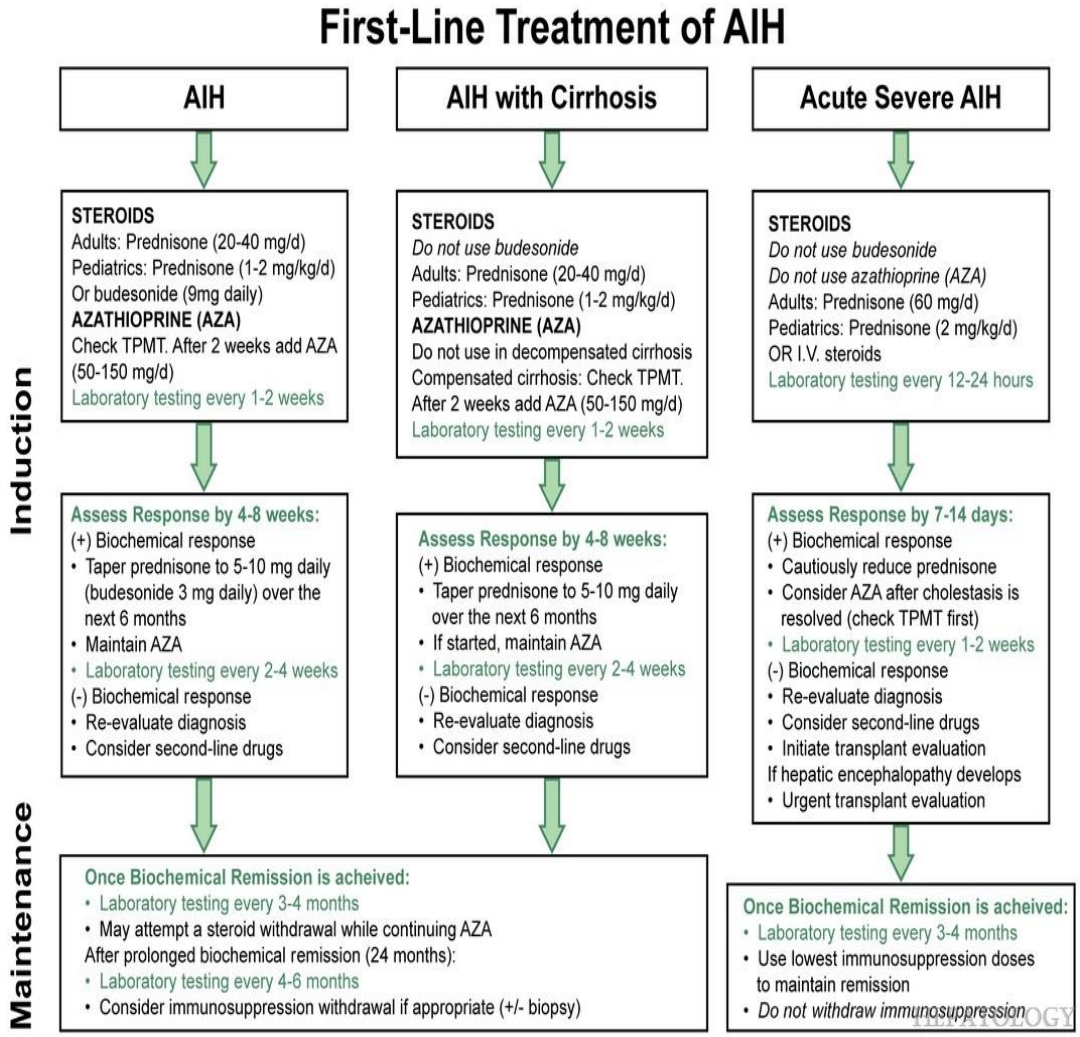
Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH
		≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Autoimmune hepatitis vs Drug Induced Liver Damage



Immune checkpoint inhibitors have been associated with immune-mediated liver injury and are frequently steroid-responsive, but the liver injury lakcs autoantibodies and typical histological features of AIH



- Goal of immuno-suppressive treatment is to achieve normal ALT and gammaglobulin levels
- Second-line therapies for treatment failure: MMF, calcineurin inhibitors (CsA,TAC), mercaptopurine and biologics (rituximab, infliximab).

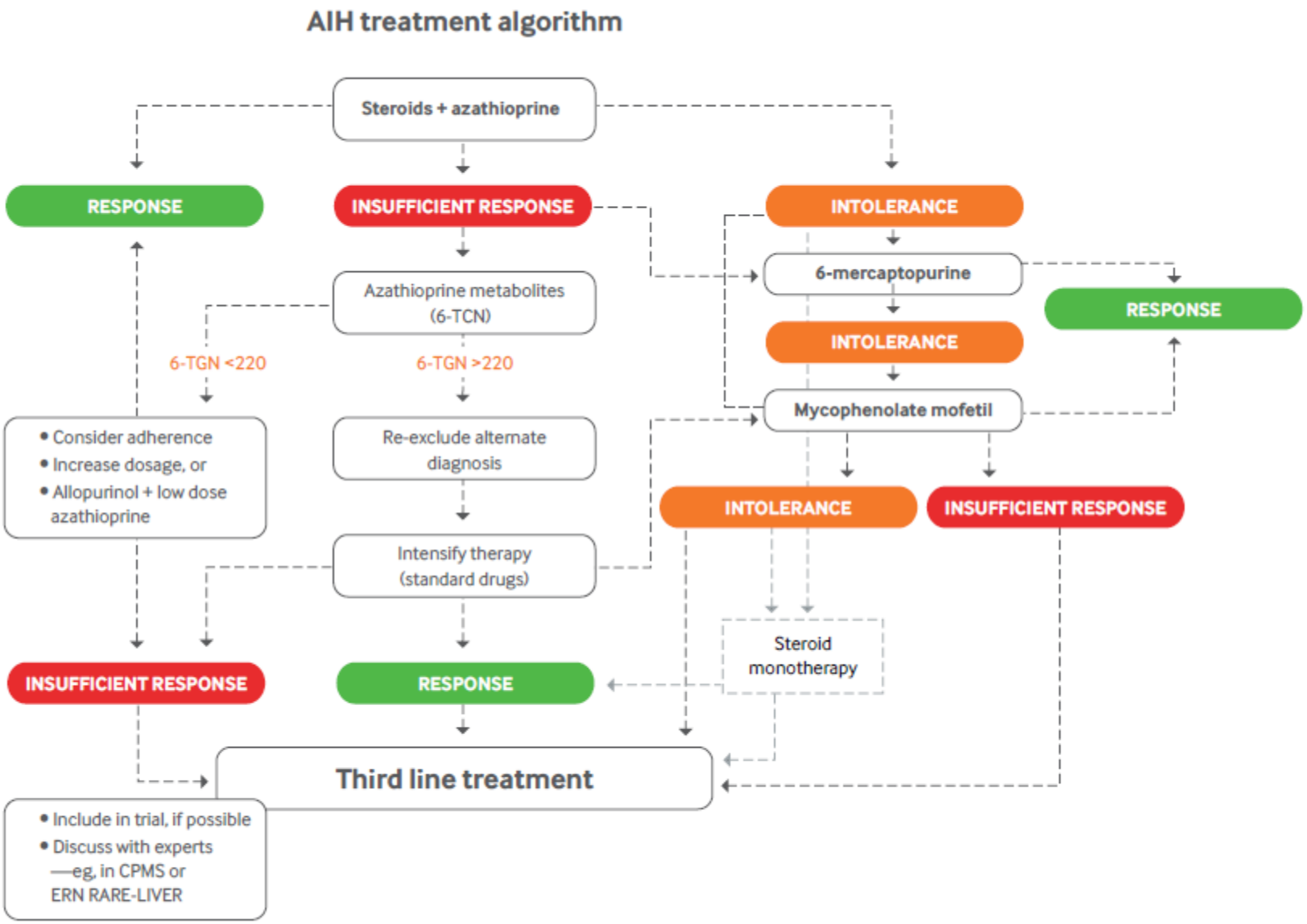


Fig 3 | Treatment algorithm for autoimmune hepatitis (AIH). 6-TGN=6-thioguanine; CPMS=clinical patient management system. Adapted from Lohse AW, et al, *J Hepatol* 2020[14]

Caso

- F del 73
- Ricovero per ittero il 18.3.23 , da una settimana dispepsia, epigastralgia, urine ipercromiche
- Assunzione di integratore a base di erbe per una 20 gg prima del ricovero , sospeso una settimana prima
- Assunzione di ibuprofen 80 mg x 2 die per 3 gg per cefalea una settimana prima del ricovero

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- AL PS : ALT 1665 AST 1929 GammGT 255 UI Bilirubina 11.9 (Dir. 9.71) mg/dl
- Non dilatazione delle VB

Caso

- PT 47% INR 1.7   piastrine 153.000/ml
- Bilirubina --- 17 (14.8 d.) mg/dl
- ALP 173 GammaGT 231 UI   LDH 332 UI
- Proteine tot 6.7g/dl Albumina 55.4 %
  Gammaglobuline 35.4%

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Pervenuta negatività markers virali, inizia 60 mg/die di metilprednisone

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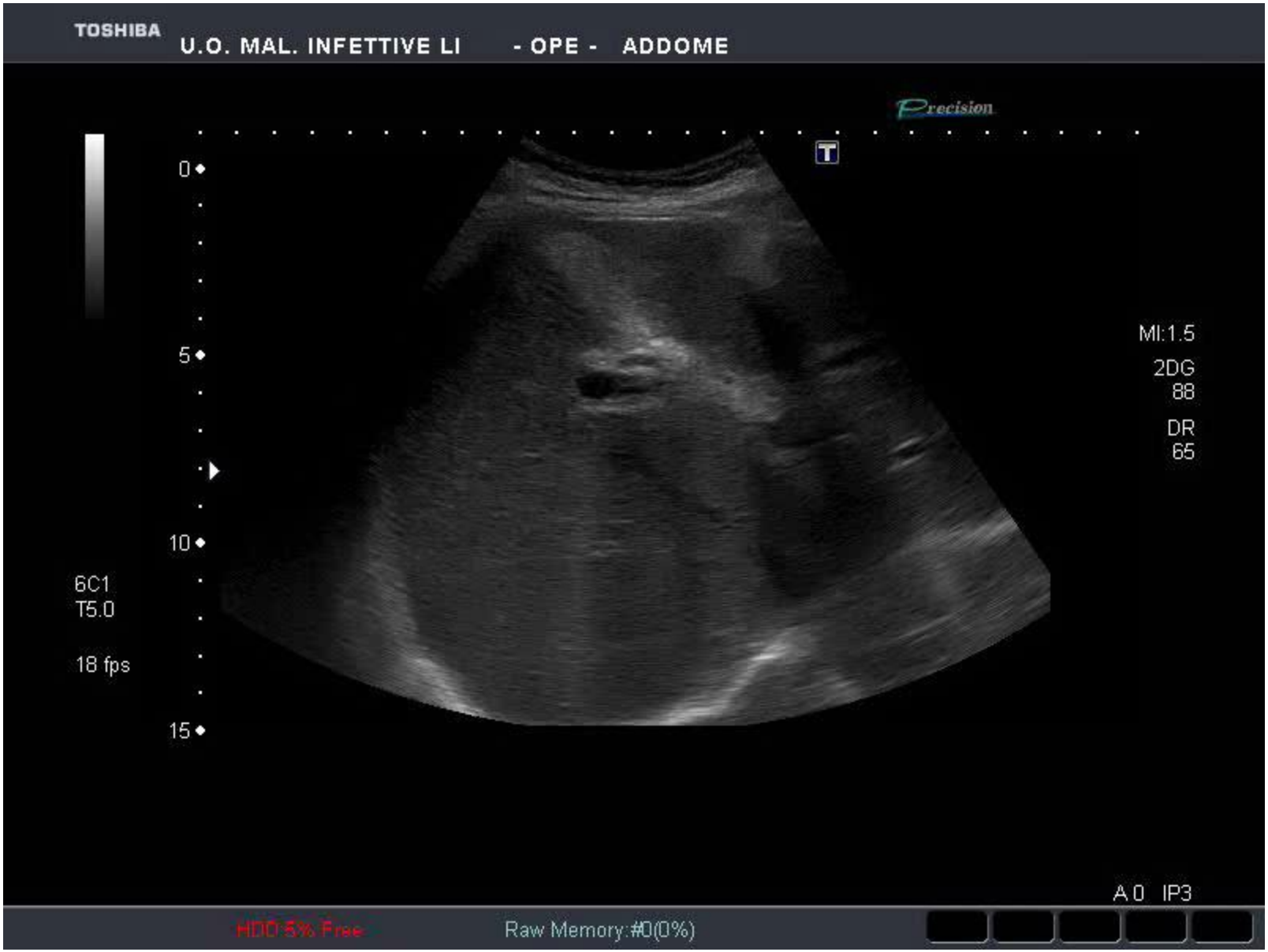
ANA positivo 1/160 Nucleare omogeneo

ASMA AMA AntiLKM1 negativi

ECOGRAFIA ADDOME

- Inspessimento diffuso delle pareti vascolari intraepatiche
- Colecisti con pareti inspessite
- Ecostruttura epatica relativamente ipoecogena
- Linfonodi reattivi del legamento epatoduodenale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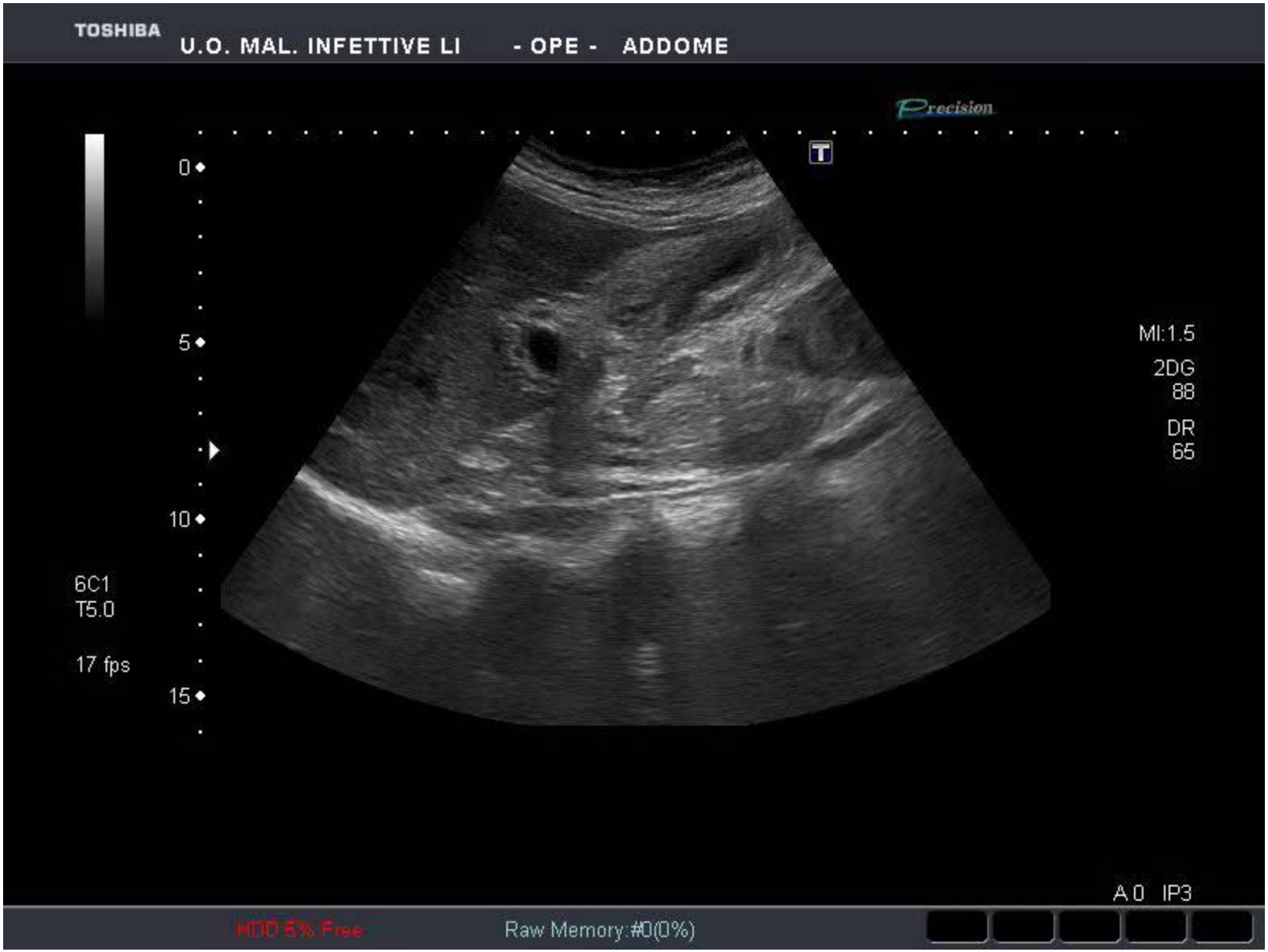
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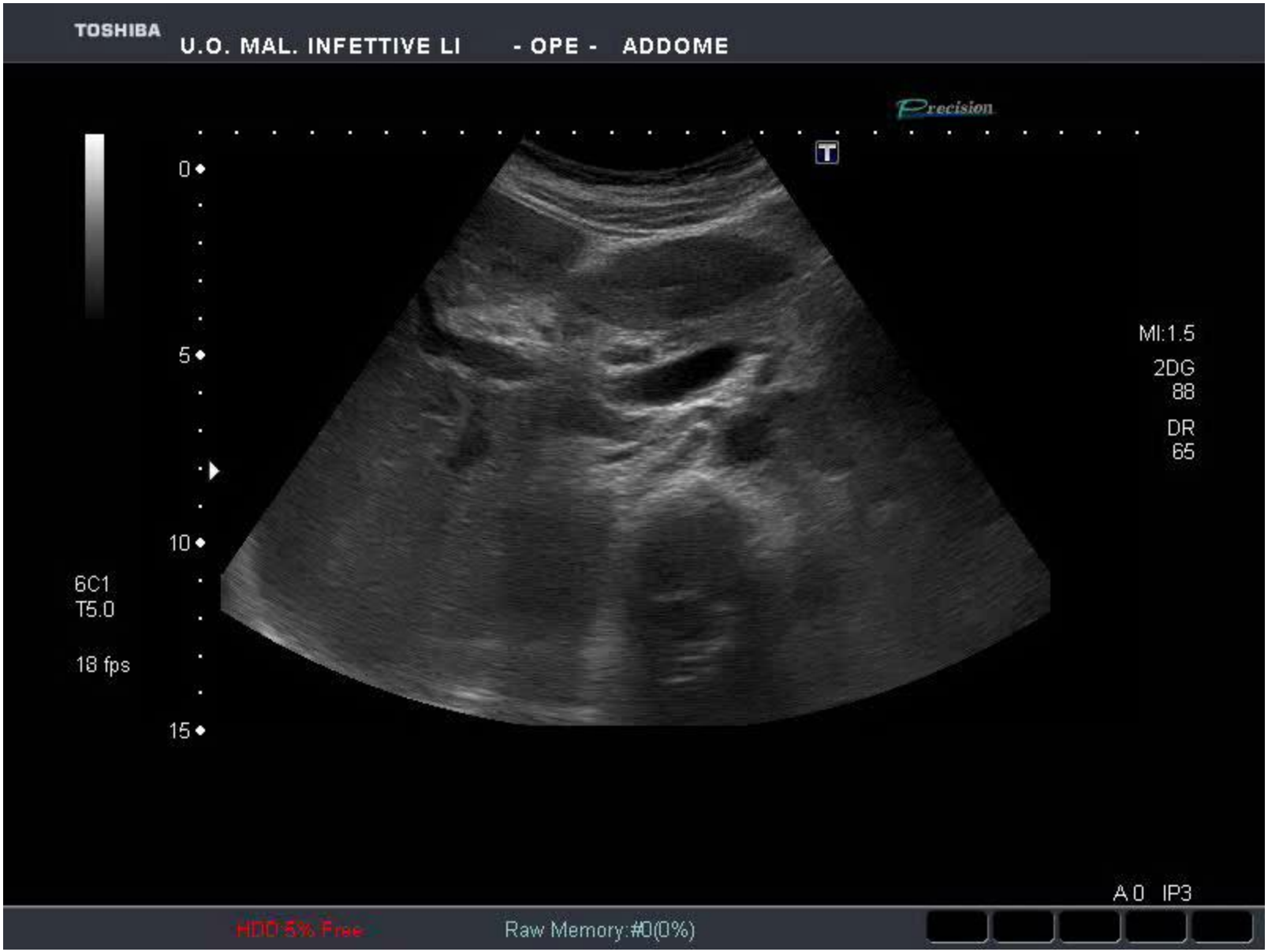
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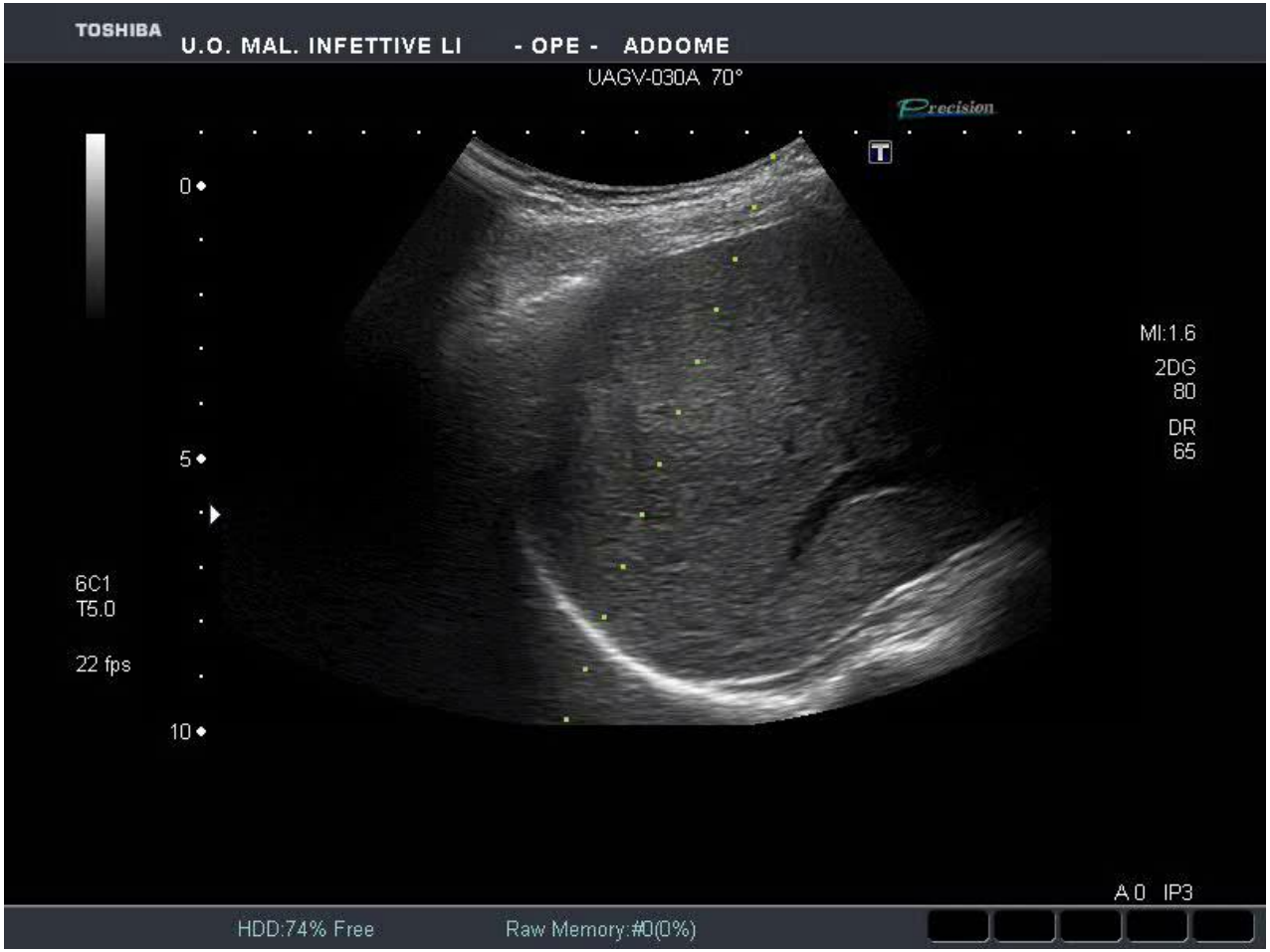

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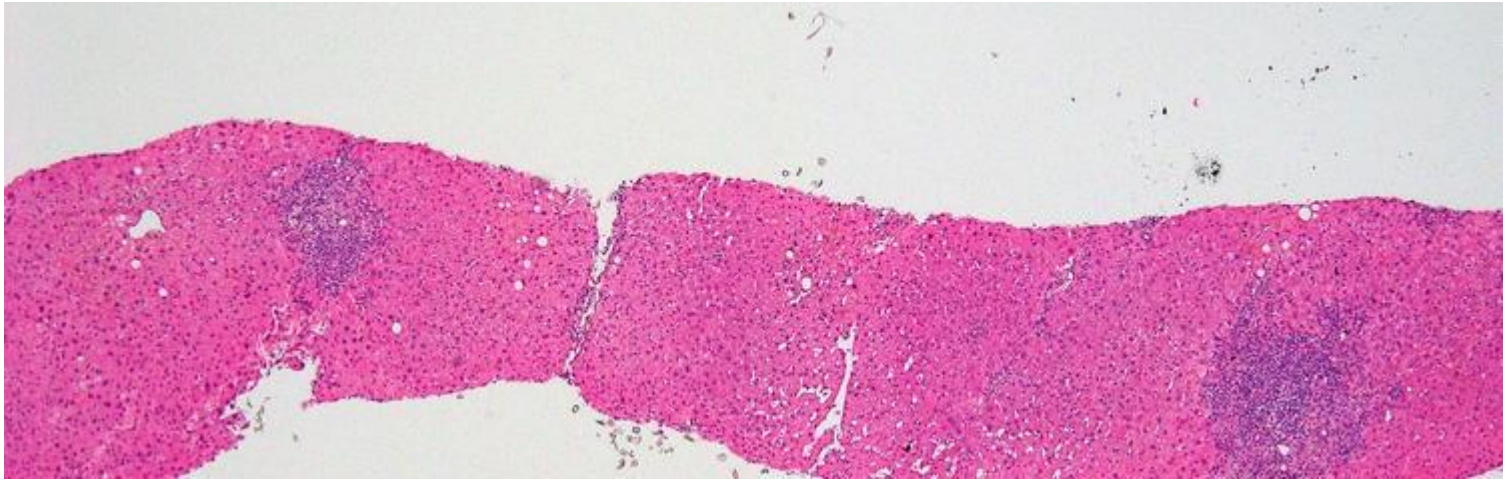
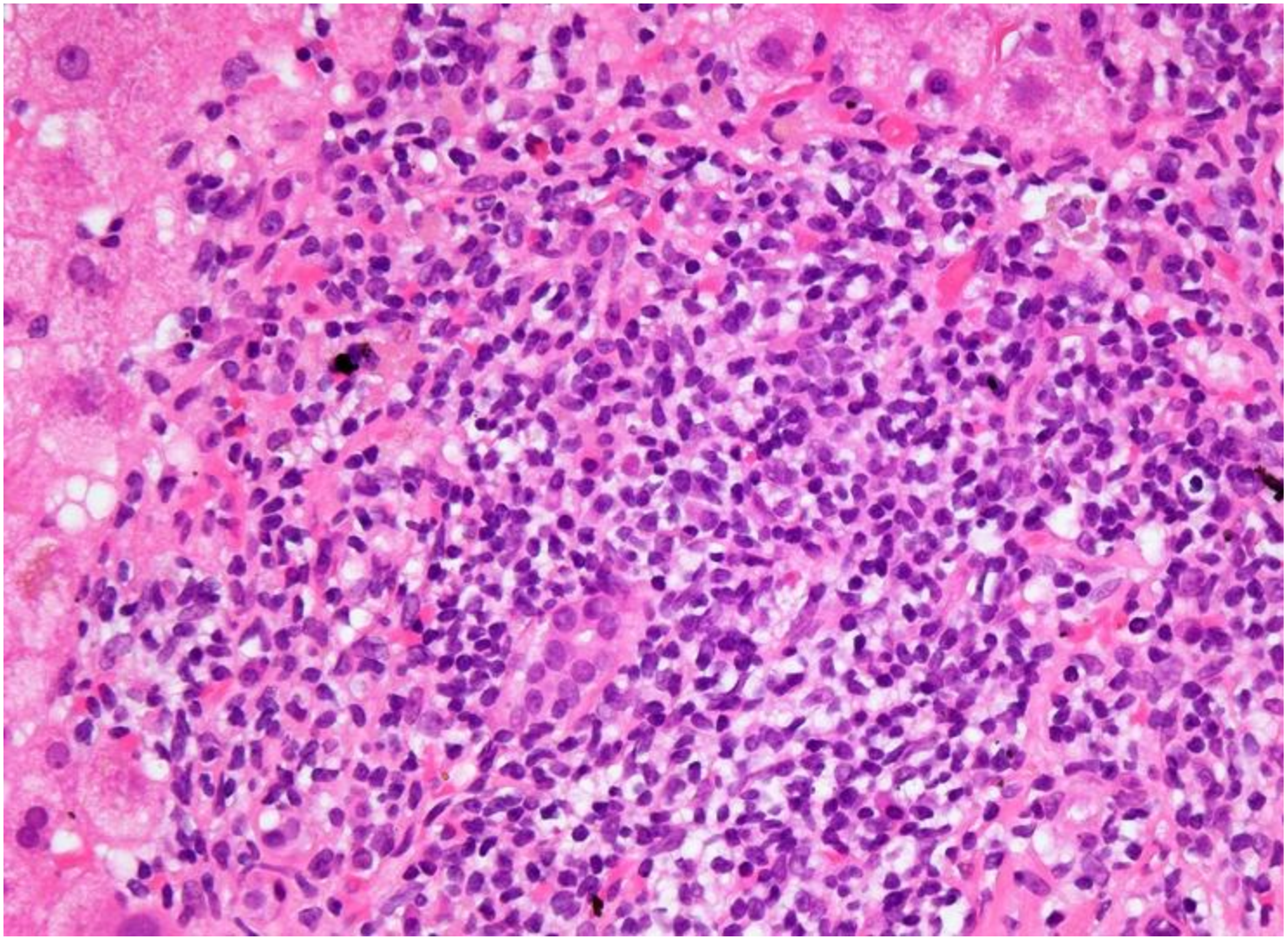
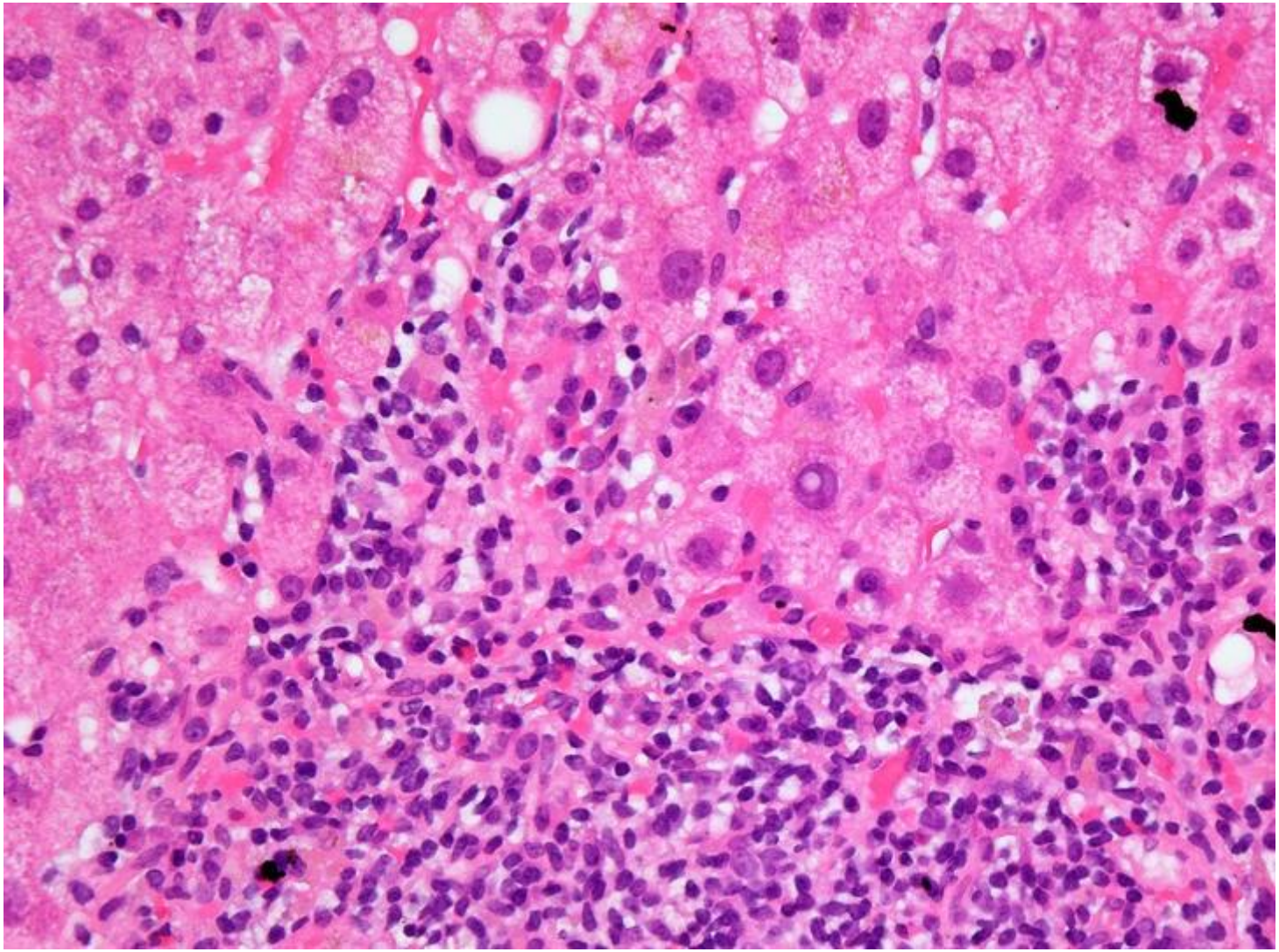


Parenchima epatico ad architettura conservata
Spazi portalri dilatati per intenso infiltrato infiammatorio con piecemal necriosis e fibrosi periportale
In sede lobulare focolai di spotty e di necrosi confluente con la formazione di ponti di necrosi porto-portali e porto-centrali
Non depositi di ferro (Colorazione di Perls)
Con la colorazione con CK 7 si evidenzia neoduttulogenesi

L'insieme dei reperto orienta per epatite autoimmune,confrontare con i dati clinici

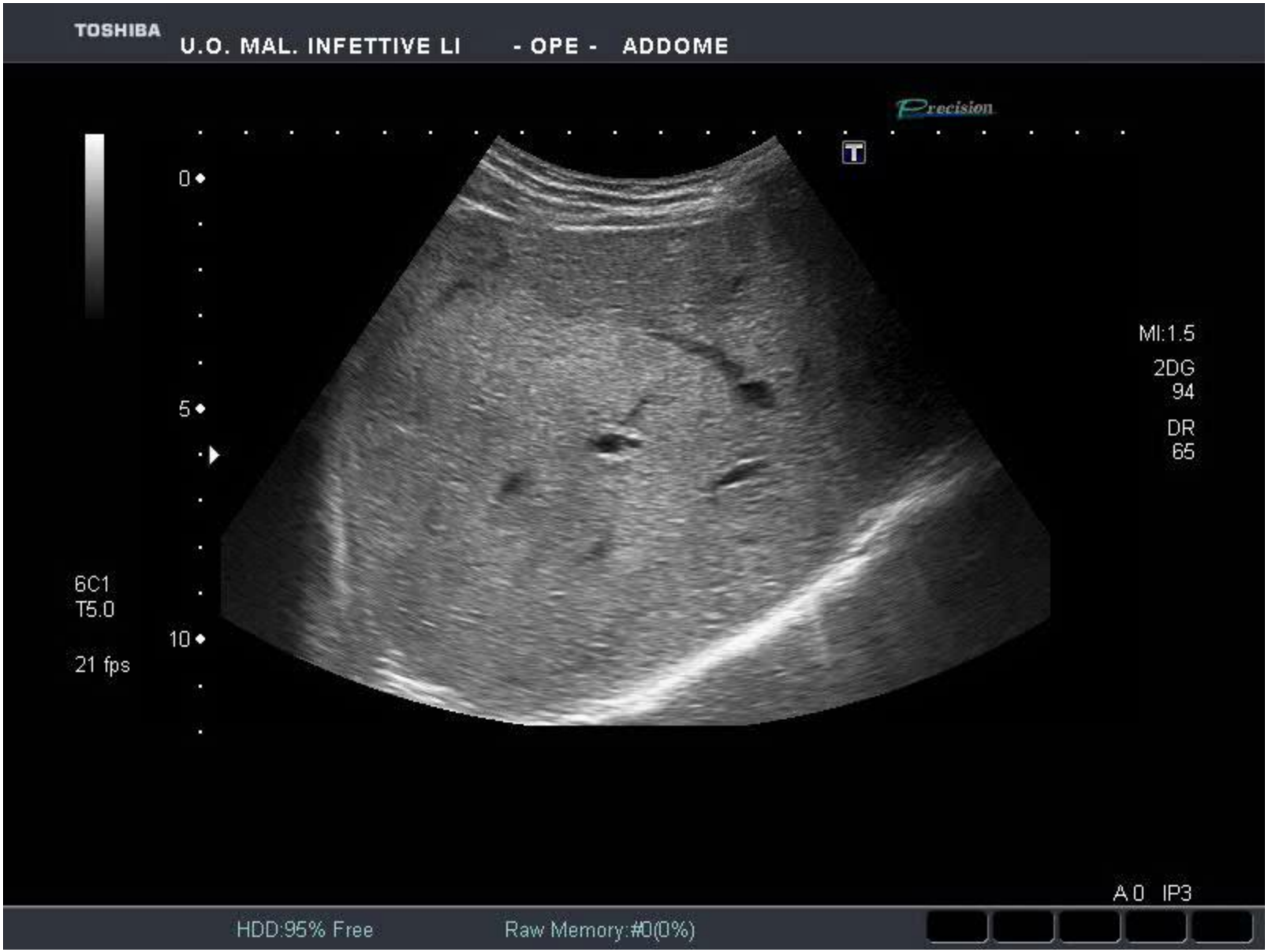




Caso

- Normalizzazione lenta dei parametri epatici
- Necessità di dosaggio elevato di steroide insieme ad azatioprina per ottenere normalizzazione esami

- Attualmente 100mg di azatioprina + 5mg di prednisone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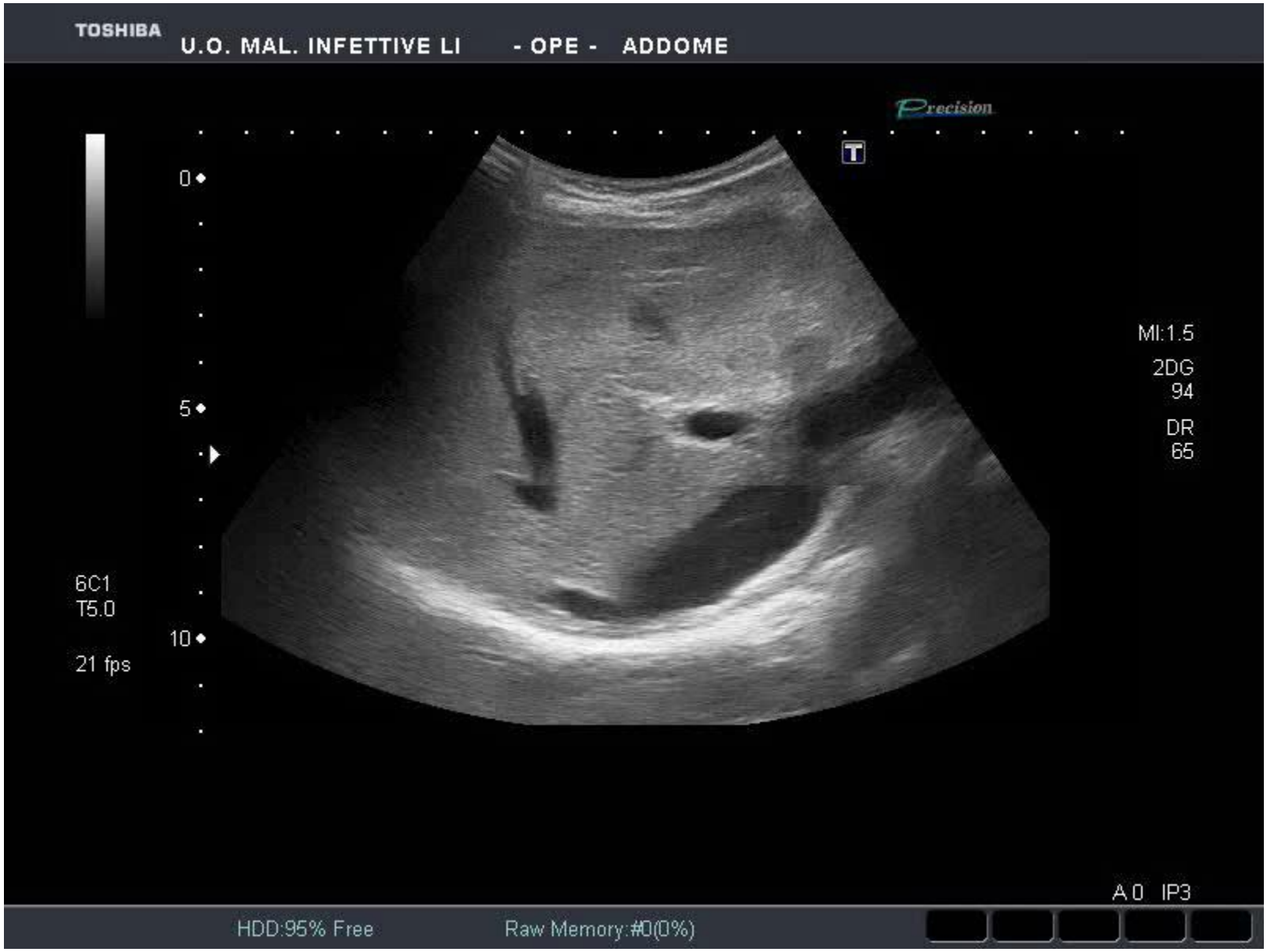
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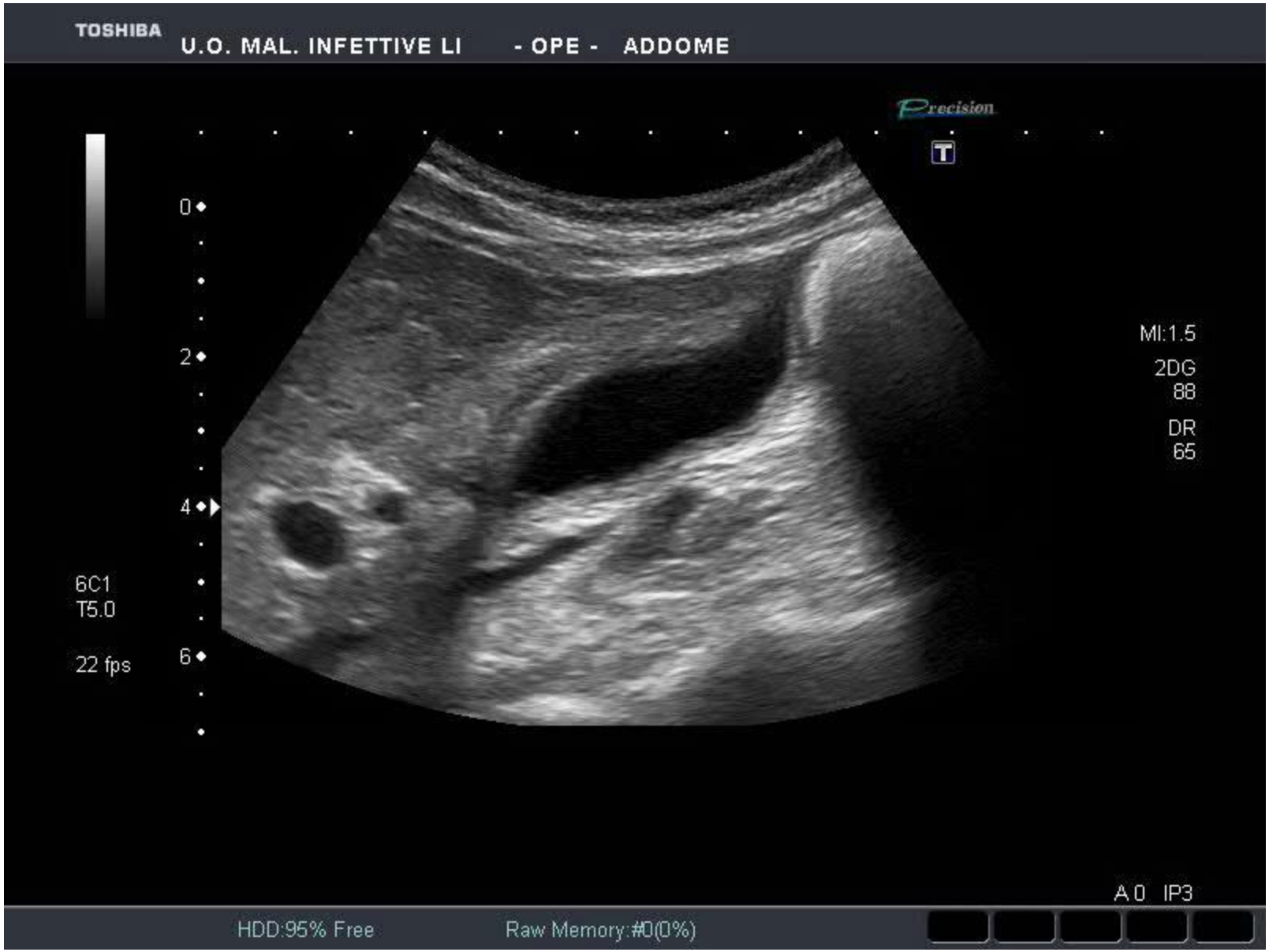
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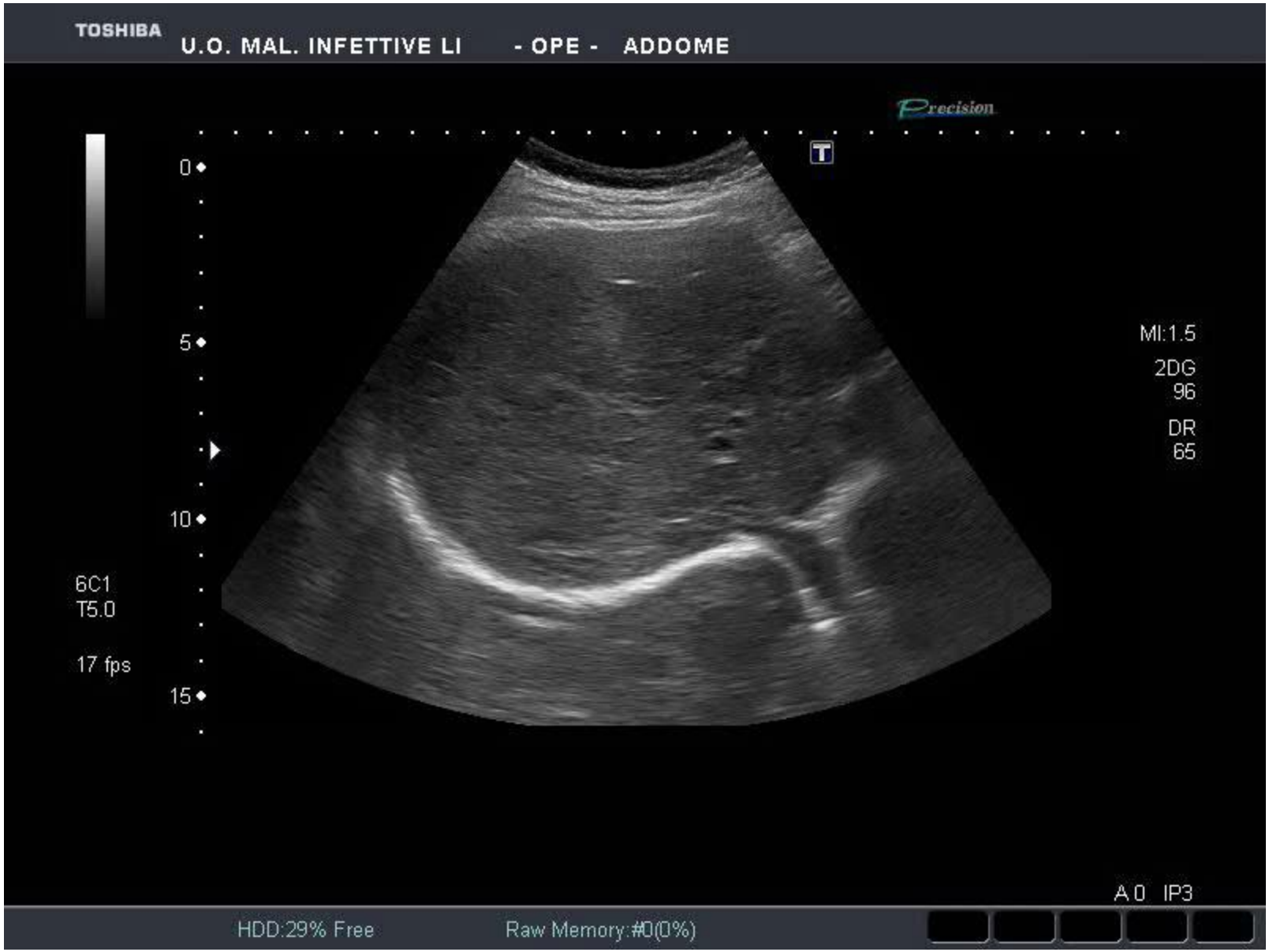
Caso

- F del 71
- Viene a valutazione il 26 gennaio ‘23 per rilievo, da circa due anni, di modesta elevazione delle transaminasi e talora di GammaGT con unico episodio documen/tato di aumento notevole (ALT > 400 UI) nel marzo ‘22.

- Ecografia addome superiore :
  Marcata disomogeneità ecostrutturale del fegato con aree di iperecogenicità a distribuzione irregolare, irregolarità del margine epatico. Non lesioni focali, vene sovraepatiche visualizzabili, microlitiasi della colecisti,non evidenza di segni di ipertensione portale


TOSHIBA
U.O. MAL. INFETTIVE LI - OPE - ADDOME
Precision
0
5
10
15
MI:1.5
2DG
96
DR
65
6C1
T5.0
17 fps
A 0 IP3
HDD:29% Free
Raw Memory:#0(0%)

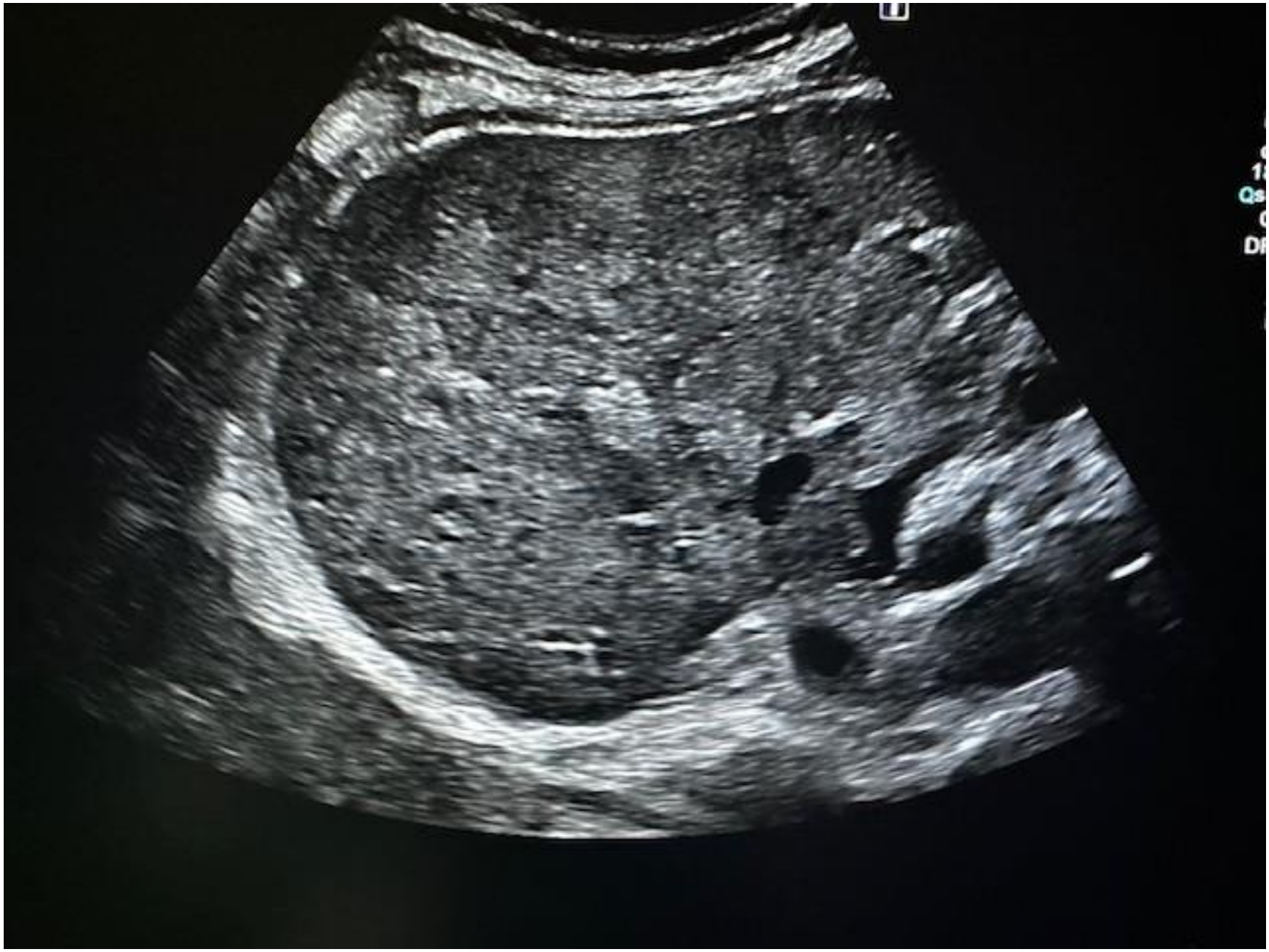
Caso

- Rivalutando tutta la storia :
- Primo rilievo di > transaminasi il 6.10.21
- Esami epatici precedenti del febbraio 2020, eseguiti per regolare controllo per tiroidite di Hashimoto in trattamento con Eutirox , e negli anni precedenti, sempre nella norma
- Dal primo rilievo valori fluttuanti. ALT max 478. GammaGT quasi sempre nella norma , ALP sempre nei limiti.

Caso

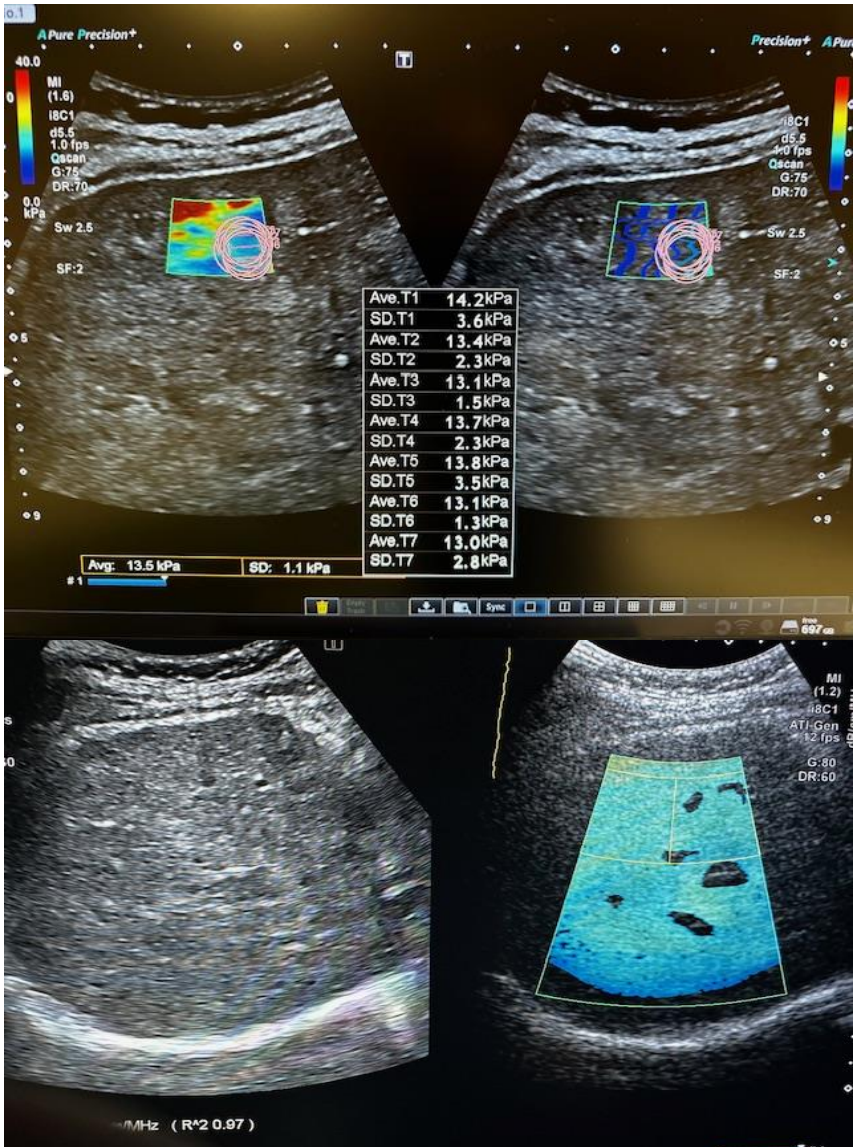
- Rivalutando tutta la storia :
- Primo rilievo di > transaminasi il 6.10.21 :
- Esami epatici precedenti del febbraio 2020, eseguiti per regolare controllo per tiroidite di Hashimoto in trattamento con Eutirox , e negli anni precedenti, sempre nella norma
- Dal primo rilievo valori fluttuanti, in media ALT tra 100 e 200, max 478. GammaGT quasi sempre nella norma , ALP sempre nei limiti.

- ANA positivo 1/160 nucleare omogeneo
- ENA., ASMA; ANCA , AMA negativi
- Modica ipercolesterolemia (200-220) trigliceridi nella norma, glicemia normale, Ferritina 219 ng/ml (max 684)
- Gamma globuline 14.4 %

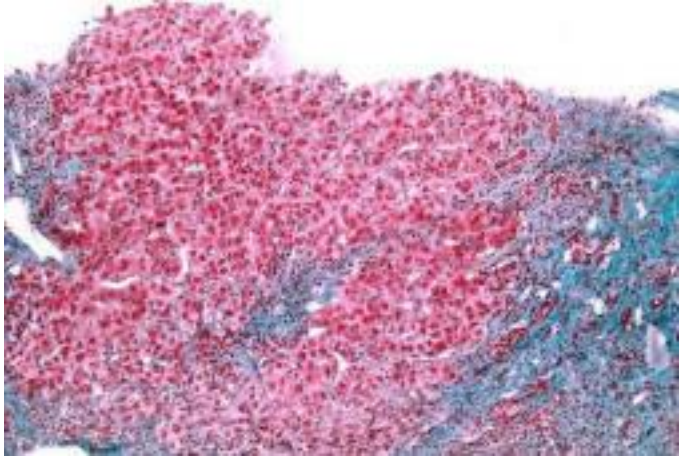


Elastosonografia

SWE 13.4 kPa SWD 18.2 ATI 0.50



- BIOPSIA EPATICA :



- *Presenza di ponti di necrosi e di fibrosi porto portali*
- *Spazi portali dilatati per intenso infiltrato infiammatorio cronico con superamento della lamina limitante e per fibrosi*
- *In sede lobulare focolai di spotty e di necrosi confluente*

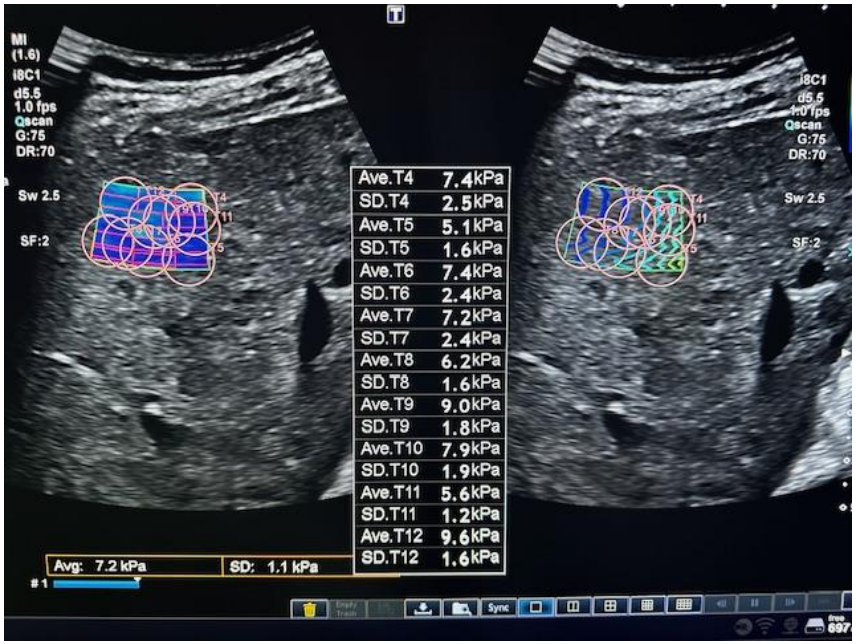
- *Con la colorazione di Perls non si evidenziano depositi di ferro*
- *Con la colorazione con CK7 si evidenzia diffusa neoduttulogenesi*

- *L'insieme dei reperti orienta maggiormente per una epatite autoimmune*

Caso

- Trattata con schema tradizionale con prednisone con successiva aggiunta di azatioprina fino a 100 mg , normalizzazione delle transaminasi con mantenimento di prednisone, oggi a 5mg

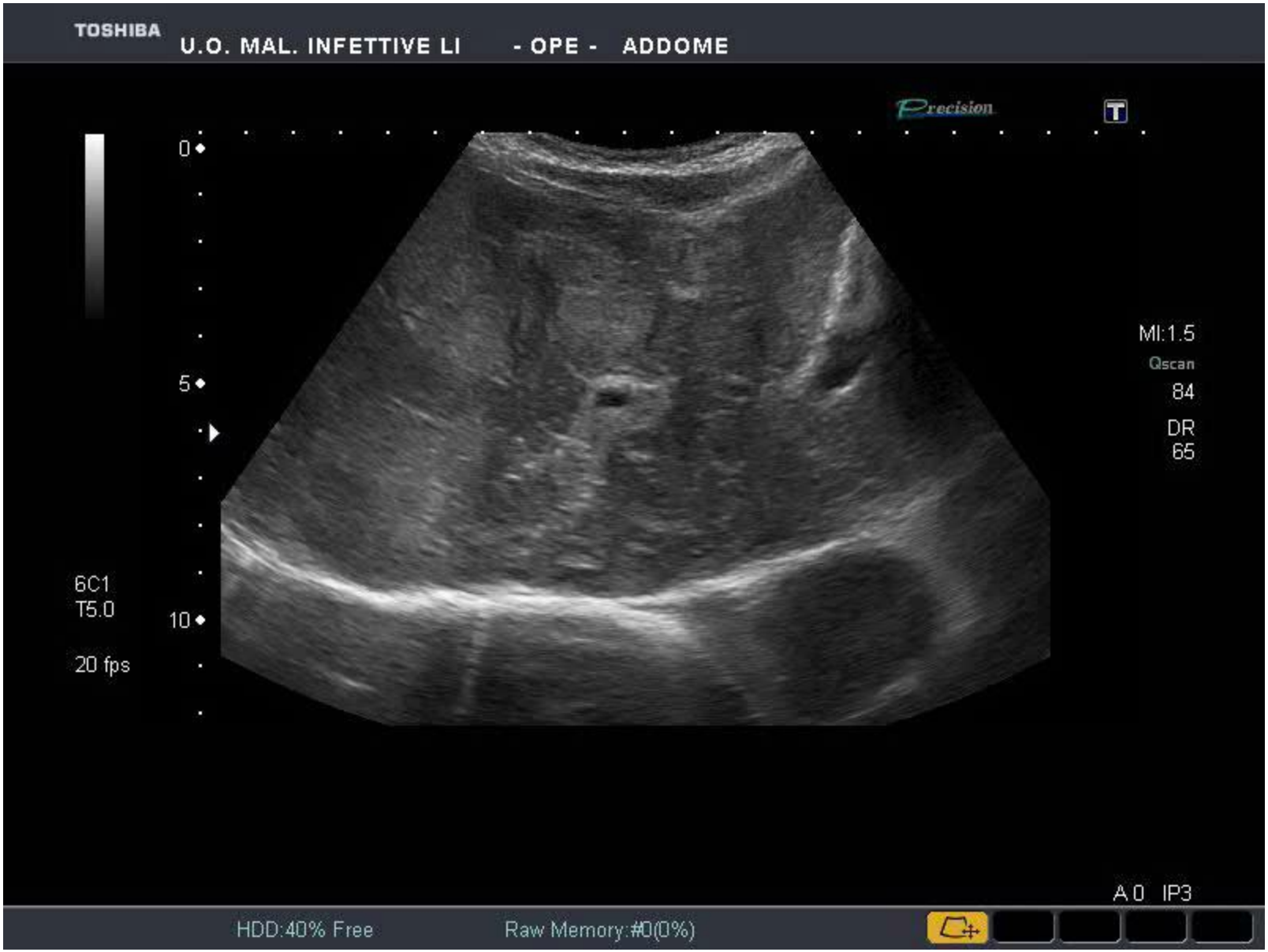
ELASTOSONOGRAFIA
SWE 7.8kPa SWE 16.5 ATI 077



Caso

- F 54 aa
- ALT 546 AST 328 GammaGT 658 ALP 327 UI
- Gammagl 31%

- ANA 1/160


TOSHIBA
U.O. MAL. INFETTIVE LI - OPE - ADDOME
Precision
0
5
10
MI:1.5
Qscan
84
DR
65
6C1
T5.0
20 fps
A 0 IP3
HDD:40% Free
Raw Memory:#0(0%)

Diagnosis and management of autoimmune hepatitis

Luigi Muratori,[1,3] Ansgar W Lohse,[2,3] Marco Lenzi[1,3]

Box 2: Negative prognostic factors in autoimmune hepatitis

- Cirrhosis at onset
- Young age at onset
- Repeated relapses of active disease on drug withdrawal
- Variant syndromes (autoimmune hepatitis-PSC, autoimmune hepatitis-PBC) and concomitant liver disease (NASH/NAFLD)
  - Ethnicity (black race)
  - Vitamin D deficiency

NASH=non-alcoholic steato-hepatitis; NASFLD=non-alcoholic fatty liver disease; PBC=primary biliary cholangitis; PSC=primary sclerosing cholangitis

BMJ 2023

Caso

- F dell’84
- Viene a valutazione nel luglio ‘18 per elevazione delle transaminasi : nel tempo ALT fluttuante tra 80-150 UI, AST <100 UI
- GammaGT e ALP nella norma
- Gammaglobuline 17.7% IgM lievemente aumentate (300 mg/dl)
- ANA AMA negativi
- Anemia sideropenica Transglutaminasi Ig A negativo
- Ecografia nella norma, piccolo linfonodo reattivo del legamento epatoduodenale

BIOPSIA EPATICA (13.12.18)

- *Parenchima epatico ad architettura conservata*
- *Alcuni spazi portali lievemente dilatati per lieve infiltrato infiammatorio cronico talora nodulare con occasionale piecemal necrosis*
- *In sede lobulare focolai di spotty, diffusa colestasi, ectasie venose e dei sinusoidi, numerosi nuclei glicogenati*
- *Con la colorazione di Perls non si evidenziano depositi di ferro*
- *Con la colorazione con CK 7 si evidenzia diffusa neoduttologenesi*

Caso

- Rapida risposta a dosaggio basso di steroide (25mg di prednisone)
- Non tollerata azatioprina

- Mantiene ad oggi 5mg di prednisone, con esami epatici nella norma, se sospende le transaminasi aumentano

Caso

- M. del 71
- In data 6.2.22 per dolore toracico insorto acutamente si reca in PS dove vengono eseguiti esami che evidenziano transaminasi elevate
- Una settimana prima 3° dose di vaccino Pfizer anti SARS-Cov2
- All'ingresso ALT 1652 AST 795 UI Bilirubina 3.33 (dir 2.75) mg/dl GammaGT 510 ALP 174 PT 96% piastrine 267.000

Caso

- M. del 71
- In data 6.2.22 per dolore toracico insorto acutamente si reca in PS dove vengono eseguiti esami che evidenziano transaminasi elevate
- Una settimana prima 3° dose di vaccino Pfizer anti SARS-Cov2
- All'ingresso ALT 1652 AST 795 UI Bilirubina 3.33 (dir 2.75) mg/dl GammaGT 510 ALP 174 PT 96% piastrine 267.000
- La sorella seguita presso la nostra UO per epatite autoimmune

Caso

- ANA positivo 1/160 Nucleare punteggiato fine e denso
- AMA negativo ASMA negativo ANCA negativo
- GammaGlobuline 21.3% IgG 1680mg/dl

Caso

- ANA positivo 1/160 Nucleare punteggiato fine e denso
- AMA negativo ASMA negativo ANCA negativo
- **GammaGlobuline 21.3% IgG 1680mg/dl**

BIOPSIA EPATICA

- *Parenchima epatico ad architettura conservata seppur con la presenza di alcuni ponti fibrosi portoportali*
- *Spazi portali dilatati per la presenza di infiltrato infiammatorio linfoplasmacellulare e con granulociti eosinofili , presenza di diffusa piecemal necrosis*
- *In sede lobulare diffusa steatosi prevalentemente microvescicolare con focolai di spotty e di necrosi confluente con formazione di ponti di necrosi porto-portale*
- *Diffusi depositi di ferro intraepatocitario e nelle cellule di Kuppfer*
- *Diffusa neoduttulogenesi*

- *L'insieme dei reperti orienta maggiormente per* ***epatite autoimmune in evoluzione fibrosa associata a steatosi***

Autoimmune Hepatitis-Like Syndrome Following COVID-19 Vaccination: A Systematic Review of the Literature

Kenneth W. Chow[1] · Nguyen V. Pham[2] · Britney M. Ibrahim[2] · Kimberly Hong[2] · Sammy Saab[2,3]

Abstract

Objectives During the summer of 2021, case reports began to emerge documenting a small number of individuals who developed autoimmune hepatitis (AIH) following COVID-19 vaccination. These cases are rare and novel, and very little is known. In our systematic review, we analyzed every published case of AIH and reviewed their characteristic findings, treatment, and outcomes.

Methods We searched PubMed, Embase, and Web of Science from December 1, 2019, to November 1, 2021. Two researchers independently extracted information from the articles about vaccine type, patient history, laboratory values, histology results, treatment regimens, and disease course.

Results Thirty-two patients developed AIH-like syndromes after receiving a COVID-19 vaccine. Jaundice was the most frequently reported symptom (81%), and 19% of patients were initially asymptomatic and presented with elevated liver enzymes found during routine bloodwork. Mean alanine transaminase, aspartate transaminase, and total bilirubin were 1231 U/L, 921 U/L, and 14 mg/dL, respectively. Anti-nuclear antibody was positive in 56%, and anti-smooth muscle antibody in 28% of patients. Steroids were used in 75% of patients. Improvement or complete resolution was seen in 97% of patients. One patient died despite aggressive steroid treatment.

Conclusion COVID-19 vaccine-induced AIH is an uncommon association with just 32 documented cases in the literature. Clinicians should be vigilant for AIH in patients who present with liver injury following vaccination. These new findings should under not deter individuals from getting vaccinated, as the benefits of vaccination far outweigh the risks. Fortunately, COVID-19 vaccine-induced AIH appears amendable to corticosteroid therapy and appears to have a favorable outcome.

Digestive Diseases and Sciences (2022) 67:4574–4580

Patient information	
Number of patients	32
Age (mean ± SD)	55.6 (± 15.3)
Gender	
Male	10 (31.3%)
Female	22 (68.8%)
Race/ethnicity	
Caucasian	6 (18.8%)
Unspecified	26 (81.3%)
Geographic location	
Australia	1 (3.1%)
Asia	3 (9.4%)
Europe	11 (34.4%)
USA	17 (54.1%)
Predisposing conditions	
History of liver disease	10 (31.3%)
History of autoimmune disease	9 (28.1%)
None of the above	18 (56.3%)
Medications	
Acetaminophen	4 (12.5%)
Statin	3 (9.4%)
Other hepatotoxic medication	12 (37.5%)

Presentation	
Symptom onset, days after 1st dose (mean ± SD)	21.1 (± 15.0)
Symptoms	16 documented, 16 not documented
Abdominal pain	2 (12.5%)
Anorexia or weight loss	4 (25.0%)
Asymptomatic	3 (18.8%)
Choluria	6 (18.8%)
Fatigue or malaise	4 (25.0%)
Fever	1 (6.3%)
Jaundice	13 (81.3%)
Pruritus	2 (12.5%)

Diagnostics	
Peak laboratory values (mean ± SD)	
Alanine aminotransferase (U/L)	1230.6 (±978.2)
Aspartate aminotransferase (U/L)	920.9 (±397.2)
Alkaline phosphatase (U/L)	296.6 (±458.0)
Bilirubin (mg/dL)	13.8 (±33.7)
Gamma glutamyl transferase (U/L)	366.3 (±252.5)
Immunoglobulin G (g/L)	23.1 (±8.4)
Antibodies	
Anti-nuclear antibody	18 (56.3%)
Anti-smooth muscle antibody	9 (28.1%)
Anti-double stranded DNA	2 (6.3%)
Other	3 (9.4%)
Liver biopsy	
Performed	26 (81.3%)
Not performed	6 (18.8%)
Eosinophils on histology	11

Treatment	
First agent	
Budesonide	1
N-acetylcysteine	2
Prednisone	11
Prednisolone	9
Unspecified intravenous steroids	2
No treatment	7
Second agent	
Azathioprine	3
Methylprednisolone	1
N-acetylcysteine	1
Therapeutic plasma exchange	1
Clinical outcomes	
Time to first improvement, days (mean ± SD)	5.5 (±4.2)
Time to resolution, days (mean ± SD)	28.1 (±14.5)
Alive	31 (96.9%)
Dead	1 (3.1%)

Autoimmune Hepatitis-Like Syndrome Following COVID-19 Vaccination: A Systematic Review of the Literature

Kenneth W. Chow[1] · Nguyen V. Pham[2] · Britney M. Ibrahim[2] · Kimberly Hong[2] · Sammy Saab[2,3]

COVID-19 vaccine-induced AIH is extremely rare and has an excellent prognosis. Clinicians should consider AIH in patients who present with jaundice or elevated liver enzymes following COVID-19 vaccination, and promptly refer to hepatology for further work-up and treatment with steroids. Laboratory values typically show a hepatocellular pattern of injury and findings suggestive of type 1 AIH rather than type 2. Presence of autoantibodies is common, but its absence cannot rule out AIH. These new findings should under no circumstances deter individuals from getting vaccinated, as the overwhelming scientific consensus remains that the benefits of vaccination far outweigh the risks.

Digestive Diseases and Sciences (2022) 67:4574–4580

Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review

Masayuki Ueno[1,2] · Hiroyuki Takabatake[1] · Junya Itakura[3] · Rio Fujita[1,4] · Takahisa Kayahara[1] · Youichi Morimoto[1]
Kenji Notohara[3] · Motowo Mizuno[1]

Abstract

Several vaccines have been developed for coronavirus disease 2019 (COVID-19) and are used worldwide. Here we report a case of severe acute hepatitis induced by COVID-19 vaccination. A 54-year-old woman received two doses of the Pfizer-BioNTech COVID-19 mRNA vaccine and an additional dose of the Moderna COVID-19 mRNA vaccine. Seven days after the third dose, she noticed fatigue, appetite loss and dark urine. Laboratory tests were consistent with severe liver injury and jaundice. Anti-smooth muscle antibody and HLA-DR4 were positive; thus, we suspected that she had autoimmune hepatitis (AIH). Intravenous methylprednisolone followed by oral prednisolone were administered. Because remission was not achieved, we performed percutaneous liver biopsy. Histologically, pan-lobular inflammation with moderate infiltration of lymphocytes and macrophages, interface hepatitis, and rosette formation were present. We regarded these findings as confirmation of the diagnosis of AIH. As she had not responded to corticosteroids, we added azathioprine. Liver biochemistry tests gradually improved, and prednisolone could be tapered without relapse of AIH. Dozens of cases of AIH after COVID-19 vaccination have been reported. Corticosteroids were effective in most cases, but some patients have died from liver failure after vaccination. This case illustrates the efficacy of azathioprine for steroid-refractory AIH induced by COVID-19 vaccination.

Clinical Journal of Gastroenterology (2023) 16:554–558

Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review

Masayuki Ueno[1,2] · Hiroyuki Takabatake[1] · Junya Itakura[3] · Rio Fujita[1,4] · Takahisa Kayahara[1] · Youichi Morimoto[1]
Kenji Notohara[3] · Motowo Mizuno[1]

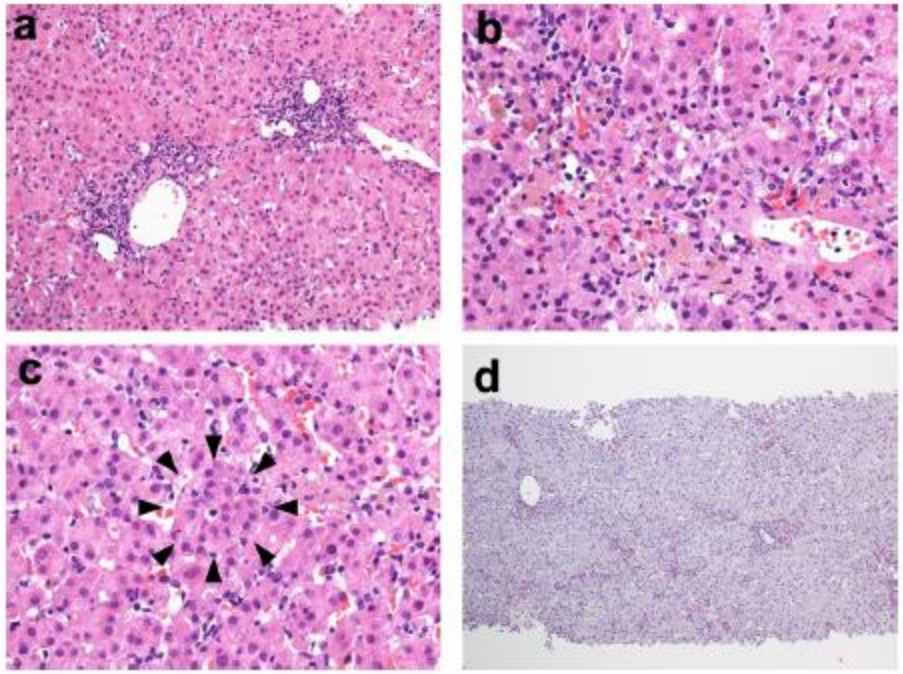


Fig. 3 Histological findings. **a** Mild infiltration of inflammatory cells with interface hepatitis are present in the periportal area. Infiltrating cells are mainly lymphocytes and macrophages. No apparent fibrosis is present (hematoxylin and eosin staining, ×20). **b** Moderate inflammation is present around the central vein (hematoxylin and eosin staining, ×40). **c** Rosette formation of hepatocytes is present (arrowheads) (hematoxylin and eosin staining, ×40). **d** Pan-lobular infiltration of macrophages containing diastase-resistant particles are present (periodic acid-Schiff-diastase staining, ×10)

Clinical Journal of Gastroenterology (2023) 16:554–558

Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review

Masayuki Ueno[1,2] · Hiroyuki Takabatake[1] · Junya Itakura[3] · Rio Fujita[1,4] · Takahisa Kayahara[1] · Youichi Morimoto[1] · Kenji Notohara[3] · Motowo Mizuno[1]

Table 1 Summary of treatment in previous case reports ($N = 45$)

Parameters	Values
Number of vaccine doses before liver injury	
One	28 (62.2%)
Two	15 (33.3%)
Three	2 (4.4%)
Type of vaccine	
Pfizer-BioNTech BNT162b2	24 (53.3%)
Moderna mRNA-1273 vaccine	12 (26.7%)
ChAdOx1 nCoV-19 vaccine	6 (13.3%)
Sinovac CoronaVac (inactivated vaccine)	2 (4.4%)
Sinopharm COVID-19 vaccine (inactivated vaccine)	1 (2.2%)
Initial therapy	
Prednisolone	22 (48.9%)
Methylprednisolone	3 (6.7%)
Budesonide	2 (4.4%)
Steroids (details not available)	2 (4.4%)
Steroids and azathioprine	2 (4.4%)
Steroids and IVIg	2 (4.4%)
Other treatment	6 (13.3%)
No treatment	5 (11.1%)
NA	1 (2.2%)
Response to initial therapy	
Present	34 (75.6%)
Absent	4 (8.9%)
NA	7 (15.6%)

Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review

Masayuki Ueno[1,2] · Hiroyuki Takabatake[1] · Junya Itakura[3] · Rio Fujita[1,4] · Takahisa Kayahara[1] · Youichi Morimoto[1]
Kenji Notohara[3] · Motowo Mizuno[1]

Additional therapy in refractory cases	
Methylprednisolone	1 (2.2%)
N-acetylcysteine	1 (2.2%)
Plasma exchange	1 (2.2%)
None	1 (2.2%)
Additional therapy for maintenance	
Azathioprine	8 (17.8%)
Steroids (e.g., prednisolone after methylprednisolone)	5 (11.1%)
None	34 (75.6%)
NA	1 (2.2%)

Clinical Journal of Gastroenterology (2023) 16:554–558

Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review

Masayuki Ueno[1,2] · Hiroyuki Takabatake[1] · Junya Itakura[3] · Rio Fujita[1,4] · Takahisa Kayahara[1] · Youichi Morimoto[1]
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Plasma exchange	1 (2.2%)
None	1 (2.2%)
Additional therapy for maintenance	
Azathioprine	8 (17.8%)
Steroids (e.g., prednisolone after methylprednisolone)	5 (11.1%)
None	34 (75.6%)
NA	1 (2.2%)

Outcome	
Improved	41 (91.1%)
Death from liver failure	3 (6.7%)
NA	1 (2.2%)

Clinical Journal of Gastroenterology (2023) 16:554–558

New-onset and relapsed liver diseases following COVID-19 vaccination: a systematic review

Abstract

Background: Liver diseases post-COVID-19 vaccination is extremely rare but can occur. A growing body of evidence has indicated that portal vein thrombosis, autoimmune hepatitis, raised liver enzymes and liver injuries, etc., may be potential consequence of COVID-19 vaccines.

Objectives: To describe the results of a systematic review for new-onset and relapsed liver disease following COVID-19 vaccination.

Methods: For this systematic review, we searched Proquest, Medline, Embase, PubMed, CINAHL, Wiley online library, Scopus and Nature through the Preferred Reporting Items for Systematic Reviews and Meta Analyses PRISMA guideline for studies on the incidence of new onset or relapsed liver diseases post-COVID-19 vaccination, published from December 1, 2020 to July 31, 2022, with English language restriction.

Results: Two hundred seventy-five cases from one hundred and eighteen articles were included in the qualitative synthesis of this systematic review. Autoimmune hepatitis (138 cases) was the most frequent pathology observed post-COVID-19 vaccination, followed by portal vein thrombosis (52 cases), raised liver enzymes (26 cases) and liver injury (21 cases). Other cases include splanchnic vein thrombosis, acute cellular rejection of the liver, jaundice, hepatomegaly, acute hepatic failure and hepatic porphyria. Mortality was reported in any of the included cases for acute hepatic failure (n = 4, 50%), portal vein thrombosis (n = 25, 48.1%), splanchnic vein thrombosis (n = 6, 42.8%), jaundice (n = 1, 12.5%), raised liver enzymes (n = 2, 7.7%), and autoimmune hepatitis (n = 3, 2.2%). Most patients were easily treated without any serious complications, recovered and did not require long-term hepatic therapy.

New-onset and relapsed liver diseases following COVID-19 vaccination: a systematic review

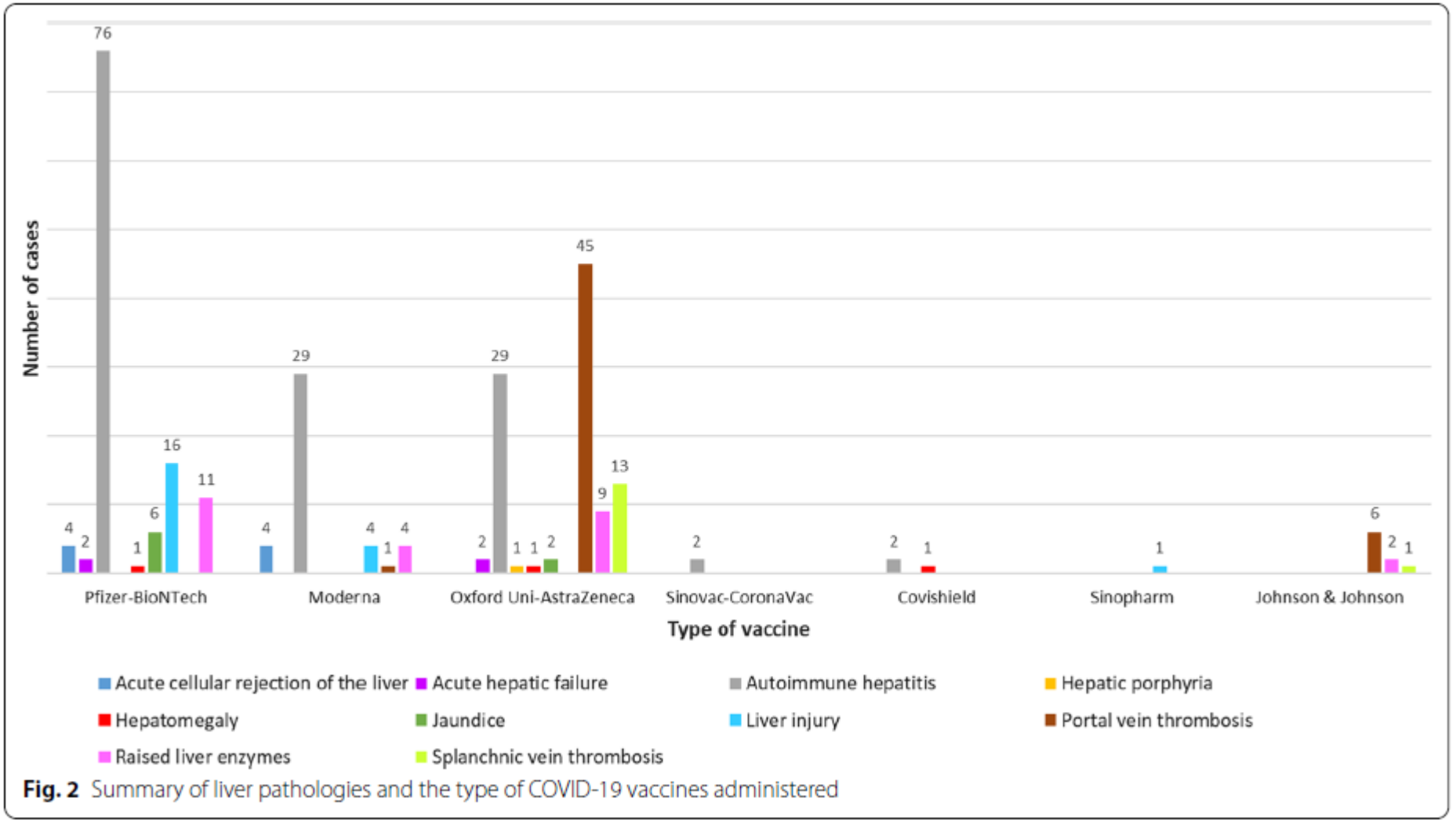

Fig. 2 Summary of liver pathologies and the type of COVID-19 vaccines administered

Immunotherapy-induced Hepatotoxicity: A Review

Da Cunha T. *et al*: *Journal of Clinical and Translational Hepatology* **2022**

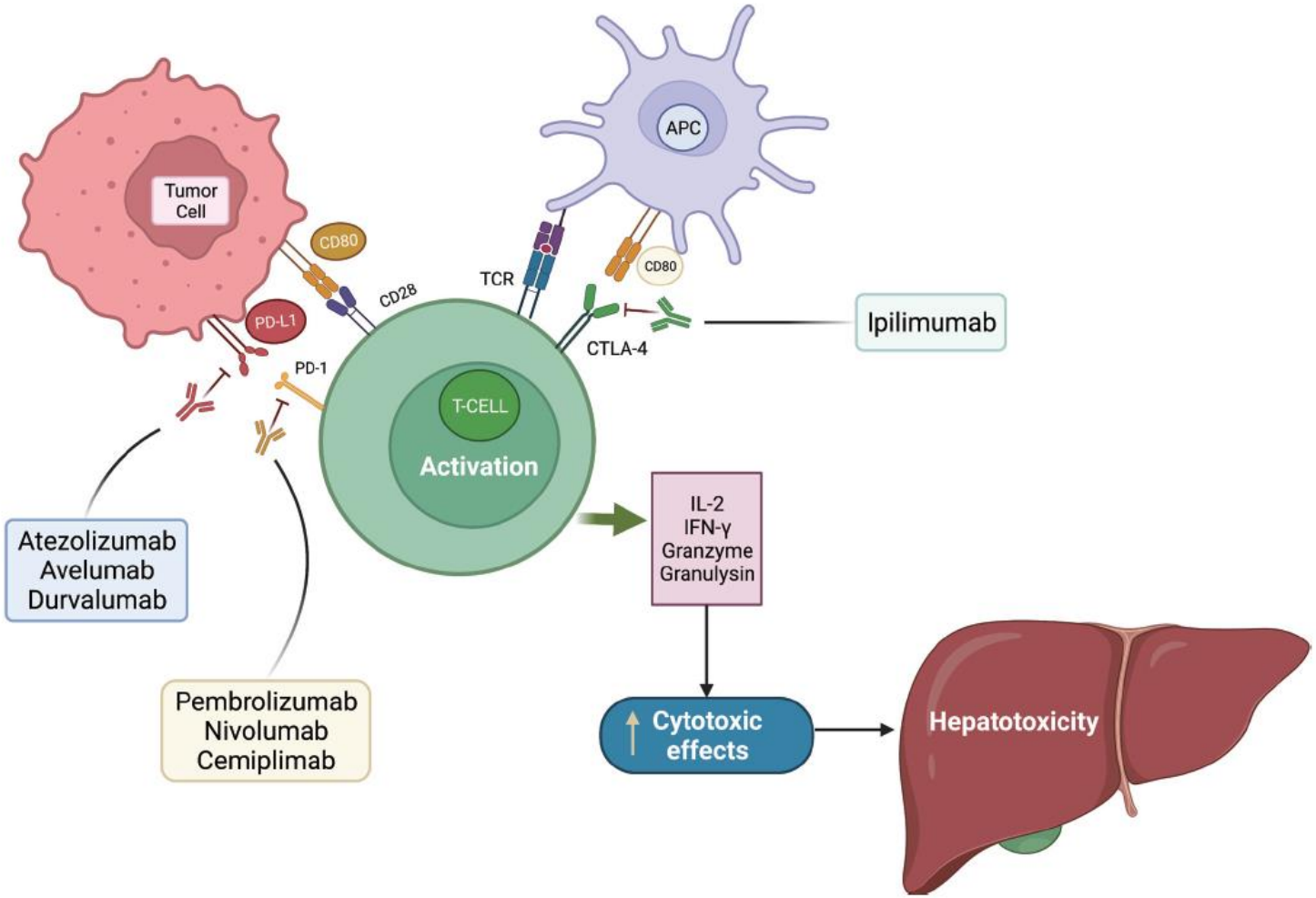

Fig. 2. Illustration of the mechanisms of action of immune checkpoint inhibitors and proposed mechanism of hepatotoxicity. APC, antigen presenting cell; PDL-1, programmed cell death ligand-1; TCR, toll-like receptor; PD-1, programmed cell death receptor-1, CTLA-4, cytotoxic T-lymphocyte-associated molecule-4.

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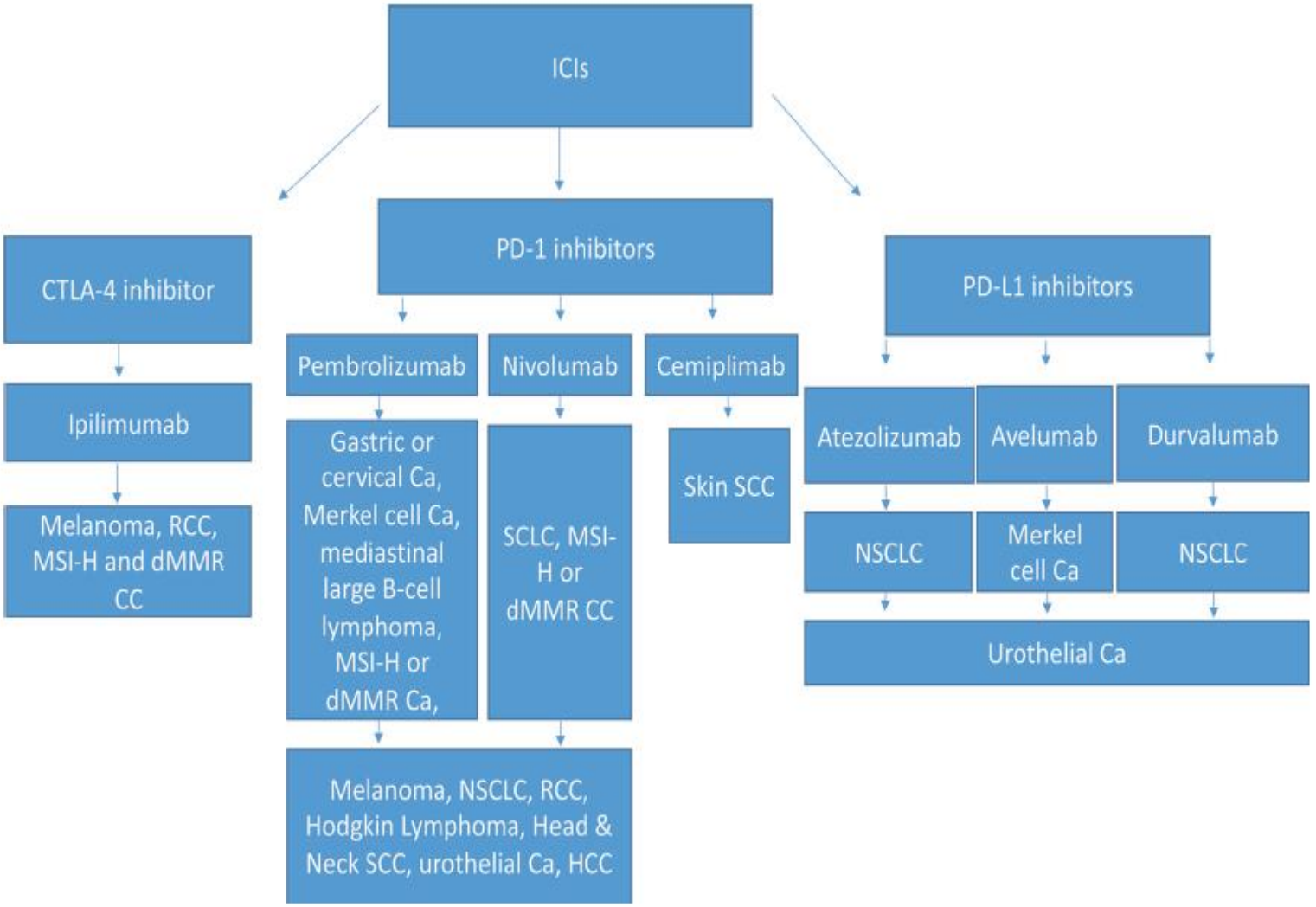


Fig. 1. Immune checkpoint inhibitors and their indications. dMMR CC, deficient mismatch repair deficiency colon cancer; HCC, hepatocellular carcinoma; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.

Immunotherapy-induced Hepatotoxicity: A Review

Da Cunha T. *et al*: *Journal of Clinical and Translational Hepatology* **2022**

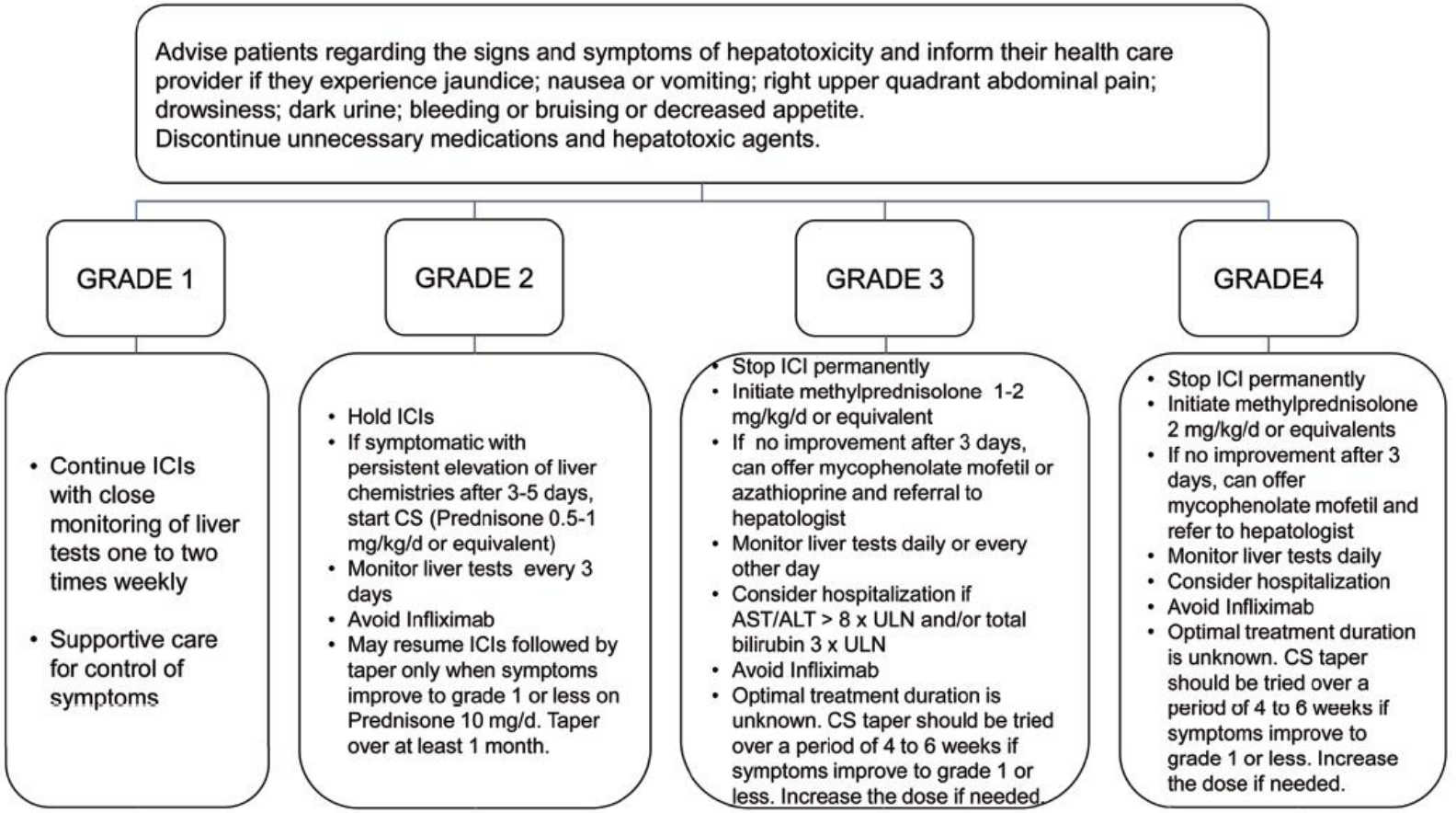
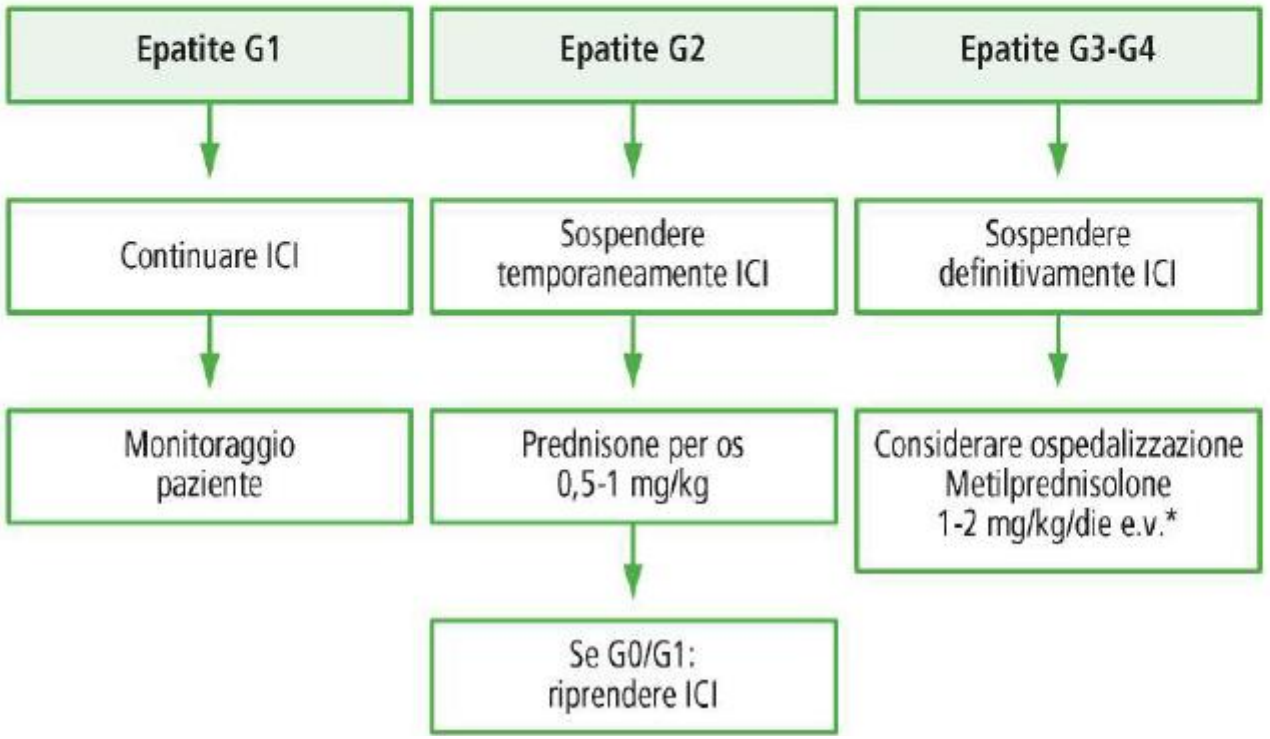


Fig. 3. American Society of Clinical Oncology management of immunotherapy-induced hepatotoxicity. ICI, immune checkpoint inhibitor; CS, corticosteroid.

ALGORITMO 8: EPATITE



**Vi sono evidenze a sostegno dell'utilizzo in pazienti steroido-refrattari di altri agenti immunosoppressori (micofenolato, azatioprina). Tali farmaci al momento della stesura della presente linea guida non sono indicati in Italia per il trattamento di epatite immunocorrelata da ICI, per cui il loro impiego in questa indicazione è da considerarsi off-label.*

Case Report

Treatment of Refractory Checkpoint-Inhibitor-Induced Hepatitis with Tacrolimus: A Case and Review of the Literature

Ruben De Wilde [1,*], Michael Saerens [1,2], Anne Hoorens [3], Anja Geerts [4] and Celine Jacobs [1]

Abstract: Immune-related hepatitis (irH) is a fairly frequent complication of immune checkpoint inhibitors (ICIs). Its management is generally based on withholding ICIs and on the rapid initiation of corticosteroids, which is successful in 63 to 96% of cases. Mycofenolate mofetil (MMF) is accepted as a second-line immunosuppressant in the case of the failure of corticosteroids. In rare cases, though, irH is also resistant to MMF and may lead to liver failure. There are no standard third-line treatments and current guidelines are based on a limited number of case reports. We present a case of a metastatic melanoma patient with an immune-related hepatitis refractory to corticosteroids and MMF, that was successfully reversed with tacrolimus. Unfortunately, this was complicated with a serious infection and progressive disease, which illustrates the complexity of treatment of steroid-refractory immunotherapy-related adverse events. Furthermore, we provided a literature review regarding the management of steroid-refractory hepatitis and proposed a strategy to circumvent the current uncertainties in the management of steroid-refractory irH.