Drug induced liver injury

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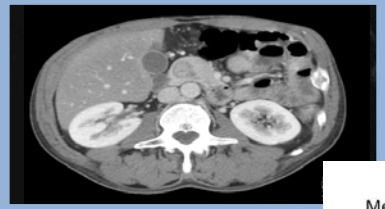


Drug induced liver injury

Hoe vaak is DILI de oorzaak van een acute hepatitis

a. 5%

b. 10%

c. 20%

d. 25%

Drug induced liver injury

Wat is de meest voorkomende oorzaak van DILI

a. Kruiden en dieetsupplementen

b. Antibiotica

c. Anti epileptica

d. Cytostatica

mevrouw Z, 16-05-1935

Voorgeschiedenis

carotisstenose beiderzijds
diabetes mellitus type 2, hypertensie
mammacarcinoom

Medicatie

Metformine 2dd 1000 mg
Losartan 1 dd 100 mg
Ascal 1 dd 100 mg
Pantoprazol 1 dd 40 mg
Amlodipine 1 dd 5mg
Atorvastatine 1 dd 10 mg

Anamnese & lichamelijk onderzoek

Recent gestart met atorvastatine
Afgenomen eetlust, vermoeidheid en gewichtsverlies
Alcohol -, geen homeopatische middelen, geen recente reizen
Sociaal: gepensioneerd, administratief werk
Familieanamnese: negatief

Lichamelijk onderzoek
Abdomen geen afwijkingen
Pitting oedeem onderbenen
Geen leverstigmata

Laboratoriumonderzoek

Hb	8.6 mmol/l
Leucocyten	7.1 x10e^{9}/L
Thrombocyten	267 x10e^{9}/L
Bilirubine	16 umol/l
Alkalische fosfatase	76 U/L
gGT	82 U/L
ASAT	163 U/L
ALAT	217 U/L
Albumine	38 g/L
INR	1.03

Laboratoriumonderzoek

Hb	8.6 mmol/l	Ferritine	200 ug/L
Leucocyten	7.1 x10e^{9}/L	IgG	13.9 g/L
Thrombocyten	267 x10e^{9}/L	IgM	1.45 g/L

Bilirubine	16 umol/l
Alkalische fosfatase	76 U/L
gGT	82 U/L
ASAT	163 U/L
ALAT	217 U/L
Albumine	38 g/L
INR	1.03

Serologie

Anti HAV IgG + / IgM –

HBsAg -, antiHBc -, anti HBs –

Anti HCV –

Immunologie

ANCA -, ANA dubieus, SMA + (1:40), LKM1 -, AMA -

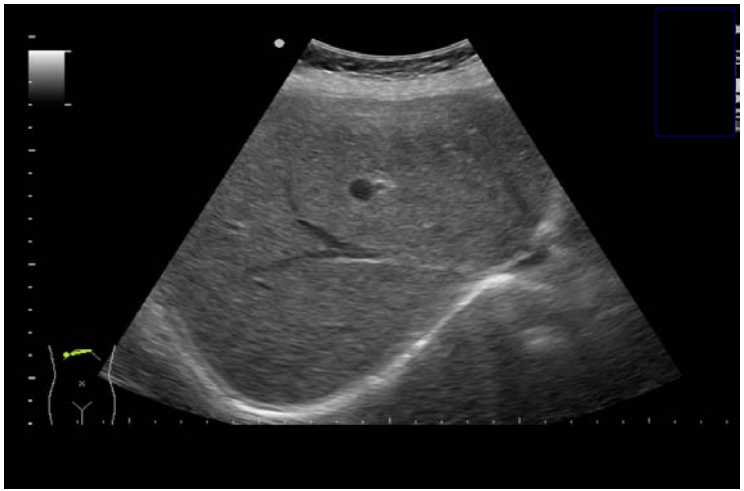
Beeldvormend onderzoek

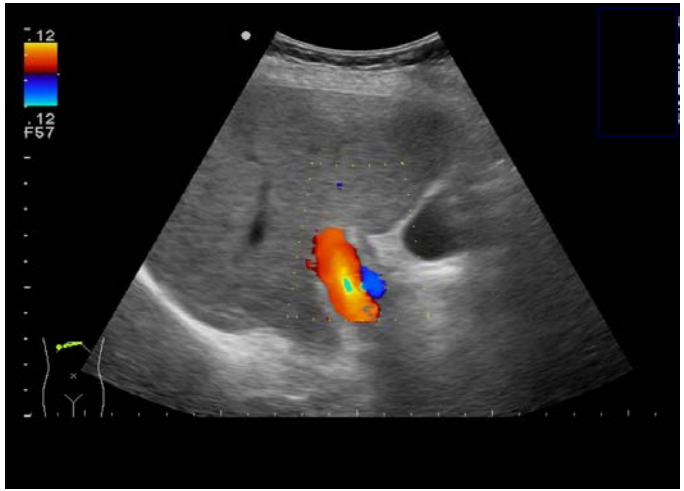
Echo abdomen

Normaal aspect pancreas.

Homogeen leverparenchym zonder focale afwijkingen of steatose.

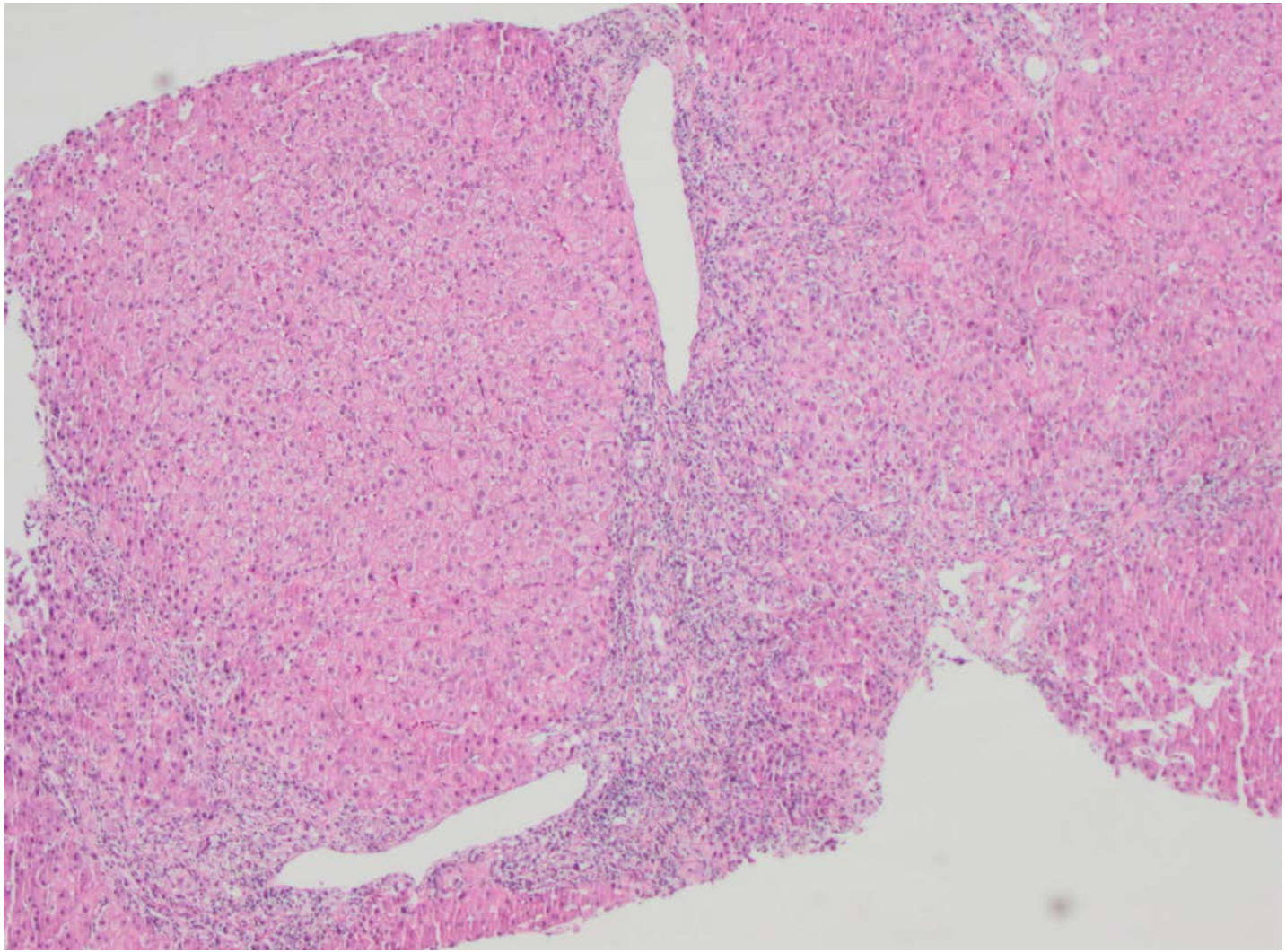
Normale galwegen, geen hepatosplenomegalie en geen ascites.

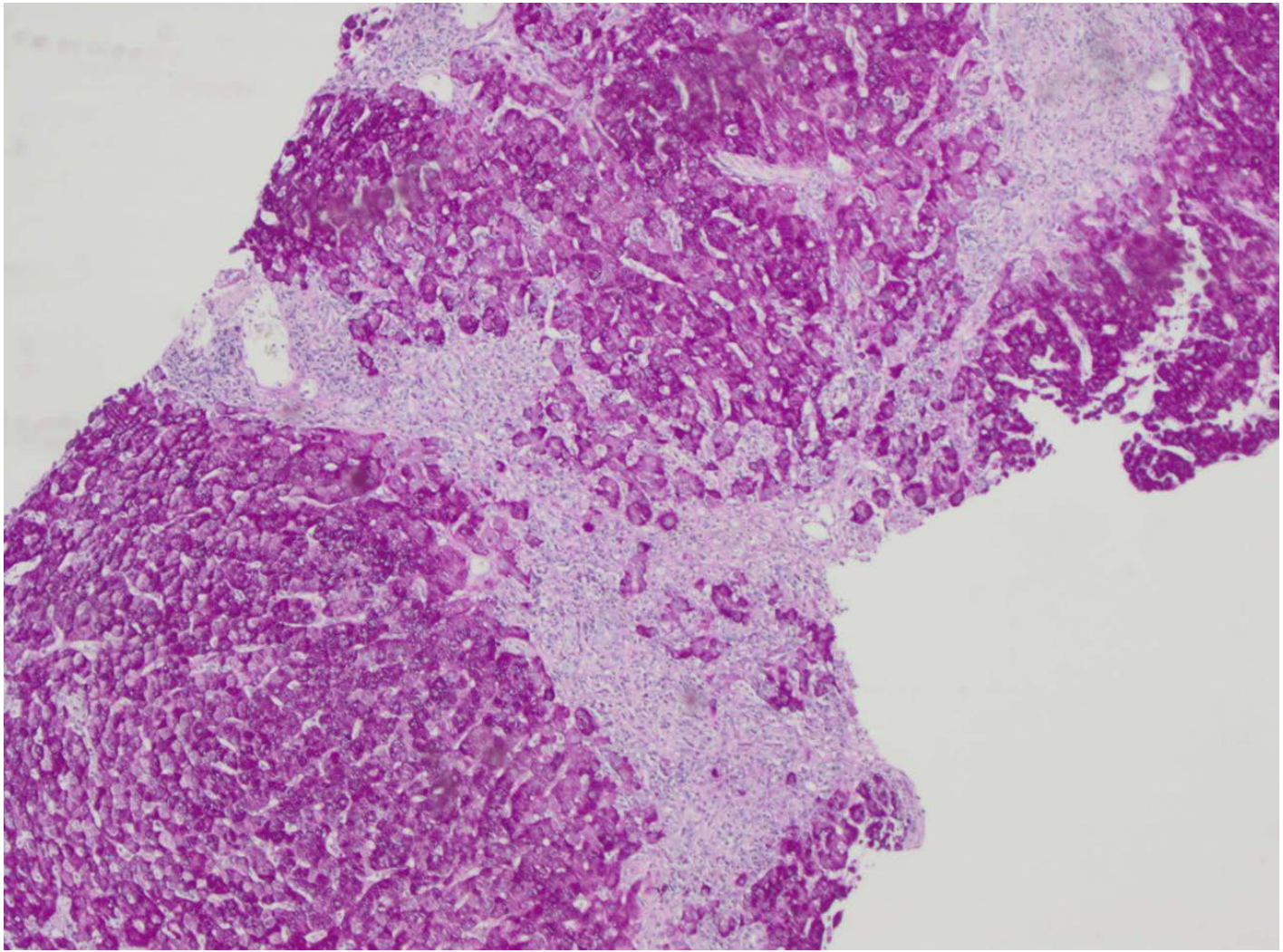


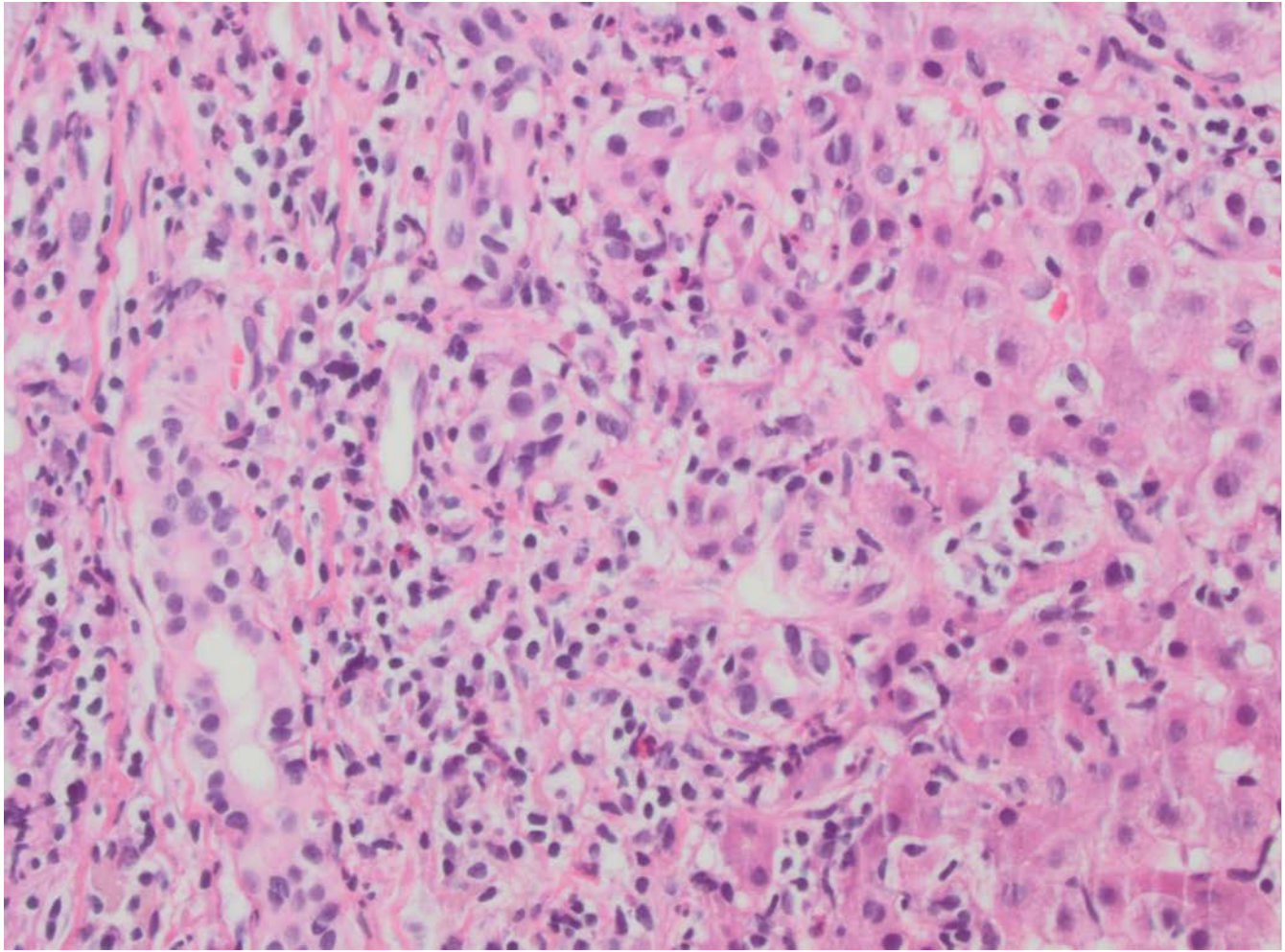


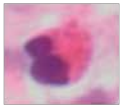
Pat Z-K

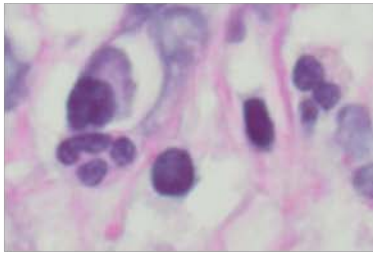
T14-14126

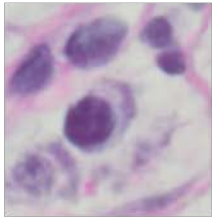


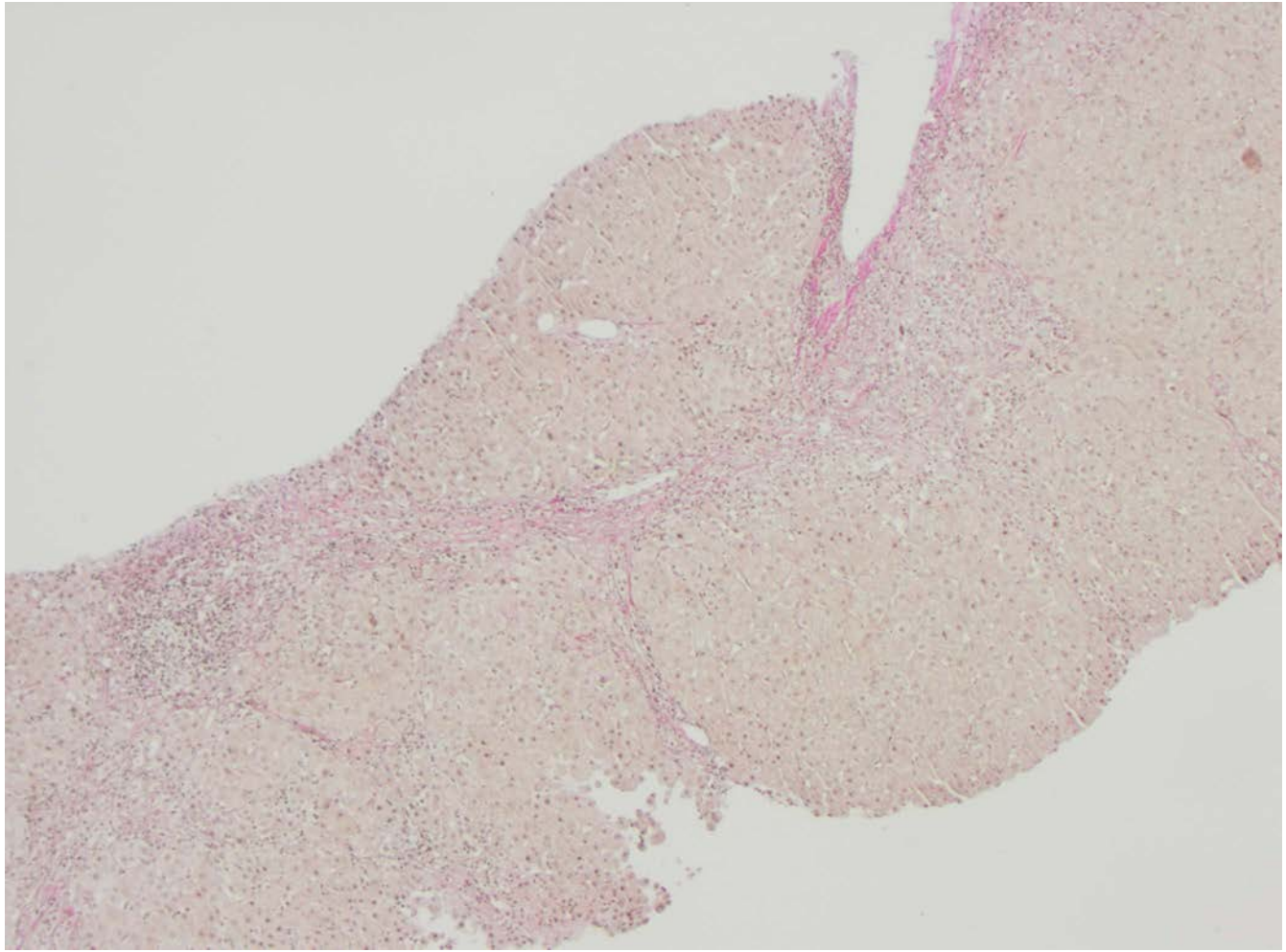


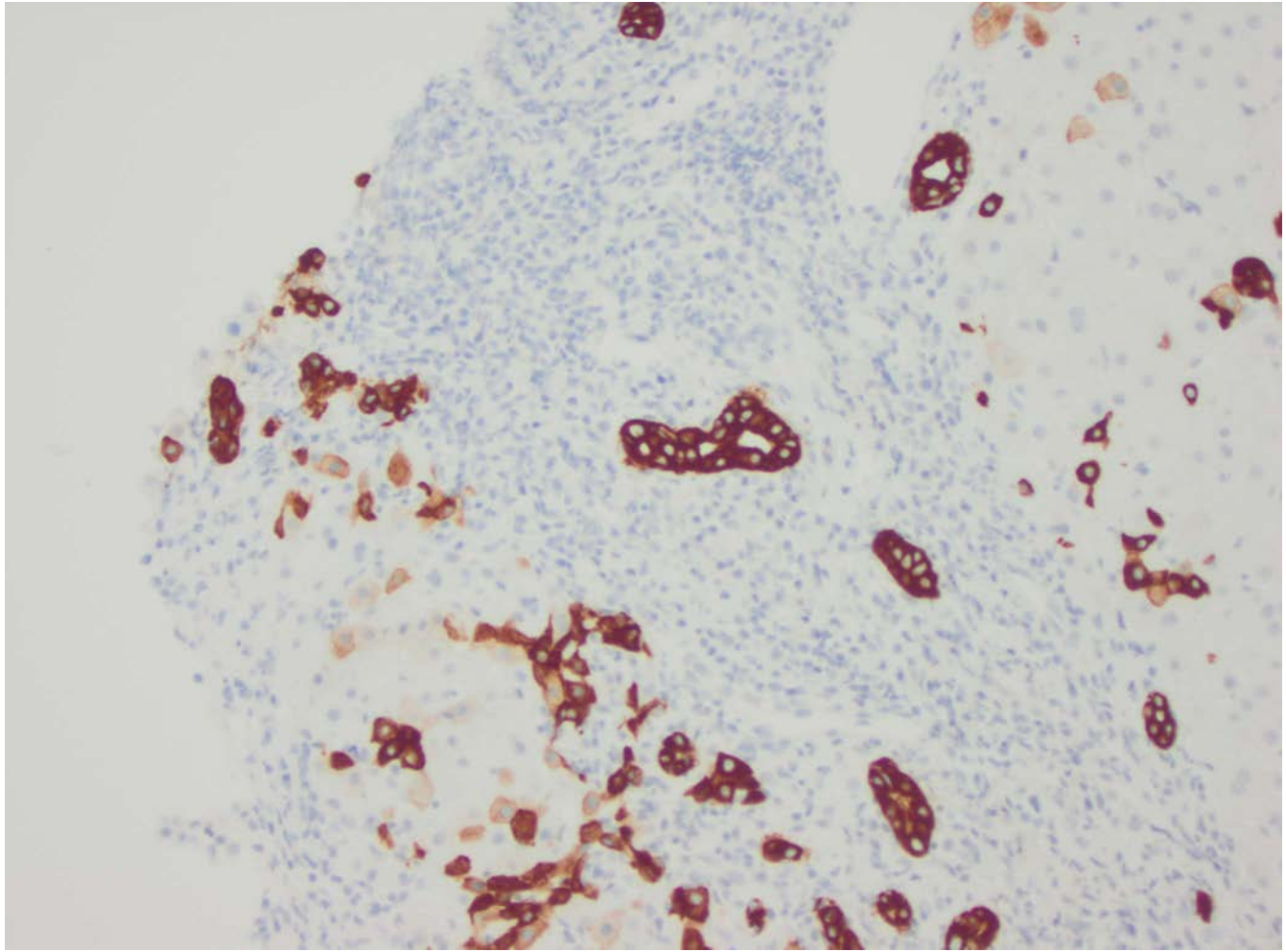










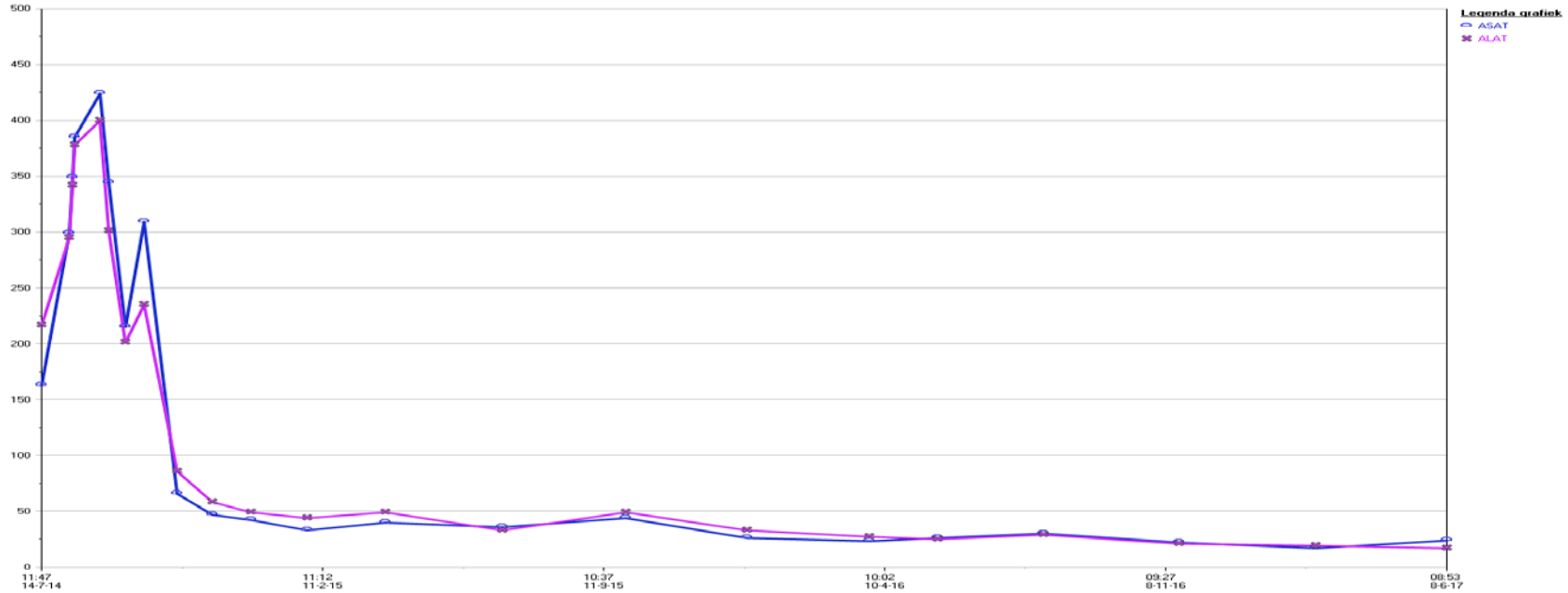


Leverbiopt: leverweefsel met ernstige **hepatitis** met portale, lobulair en interfase activiteit. Het beeld past goed bij **auto-immuunhepatitis, dd AIH-like toxisch hepatitis bij statines**.

Er is hooguit **recente fibrose**, mogelijk reversible in de tijd!

Beloop

Atorvastatine gestaakt, later gestart met budesonide en azathioprine



ATORVASTATINE & DILI

- Hepatocellulair patroon, cholestatische hepatitis
- Onset toxiciteit: 1 maand – jaren (<< 6 maanden)
- 1/3 auto immuunfenomenen (ANA, IgG, AIH features biopt)
  klein deel patiënten behandelt met immuunsuppressiva (trigger?)
- Self limiting (< 4 mnd), acuut leverfalen zeer zeldzaam
- Rechallenge vermijden, switch naar andere statine

Perdices et al. Rev. Esp Enferm Dig 2014;106:246
www.livertox.nih.gov

Dhr. W, 04-11-1949

Overname in verband met icterus & licht gedilateerde CBD

Voorgeschiedenis: erysipelas waarvoor flucloxacilline

Medicatie: geen

Laboratoriumonderzoek

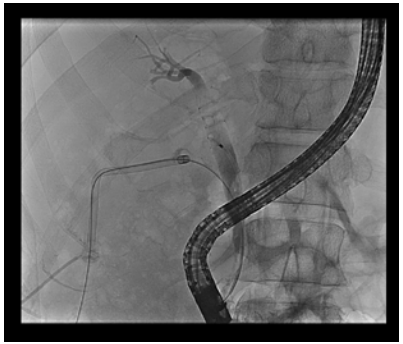
Bilirubine	345 umol/l	ALAT	142 U/L
Alkalische fosfatase	341 U/L	Albumine	29 g/L
gGT	-	INR	1.3
ASAT	64 U/L		

Beloop

ERCP: canulatie CBD niet gelukt, fausse route

Plaatsing in-uitwendige drain via galblaas

Rendez vouz procedure met plaatsing biliaire endoprothese => drainage.



Laboratoriumonderzoek

Bilirubine	458 umol/l
Alkalische fosfatase	1822 U/L
gGT	-
ASAT	266 U/L
ALAT	286 U/L
Albumine	21 g/L
INR	1.29

Laboratoriumonderzoek

Bilirubine	458 umol/l	**Serologie**
Alkalische fosfatase	1822 U/L	HAV / HCV negatief
gGT	-	HBsAg -, anti Hbs +, anti HBc +
ASAT	266 U/L	CMV/ HSV -
ALAT	286 U/L	
Albumine	21 g/L	
INR	1.29	

Laboratoriumonderzoek

Bilirubine	458 umol/l	**Serologie**
Alkalische fosfatase	1822 U/L	HAV / HCV negatief
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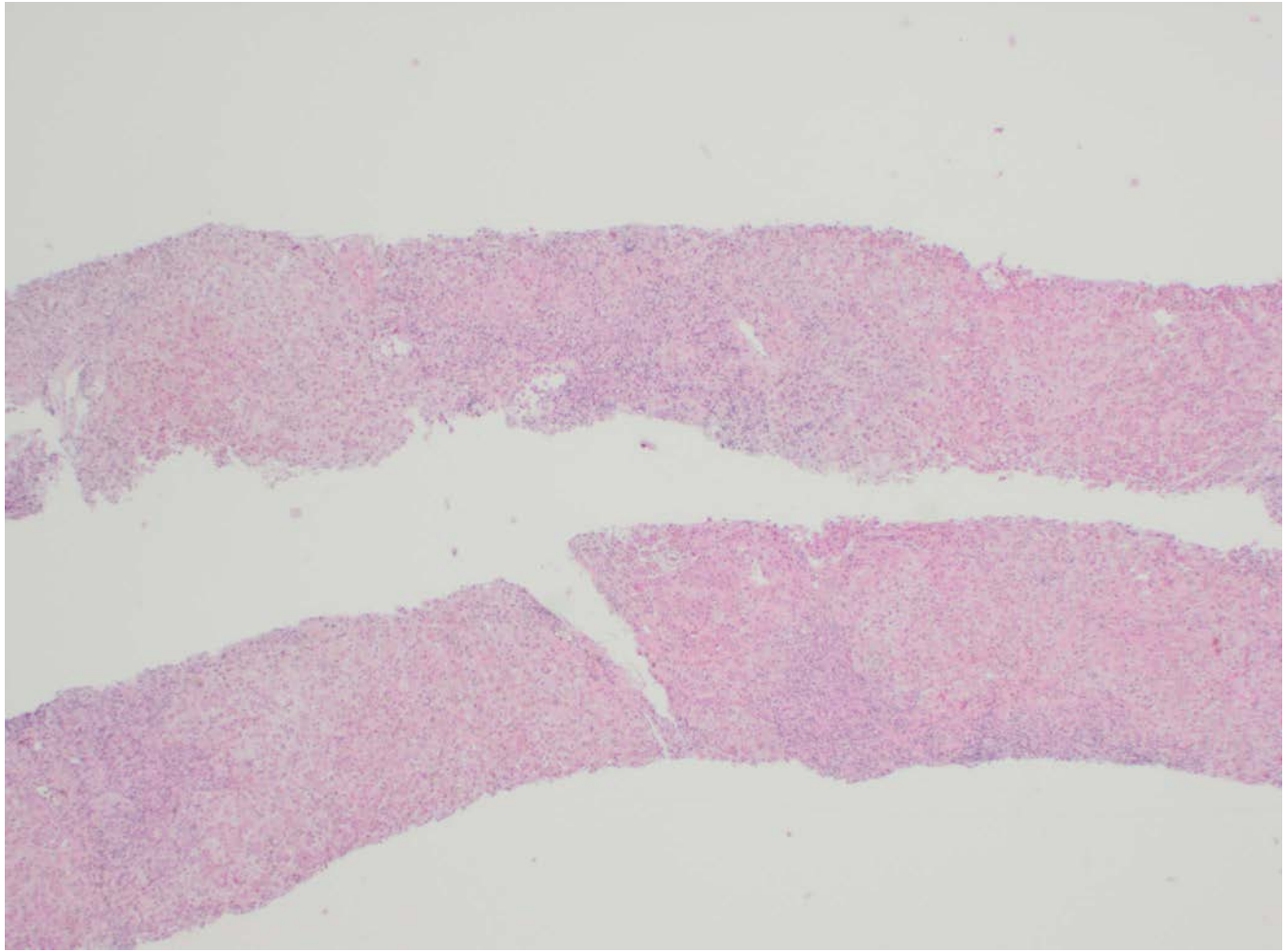
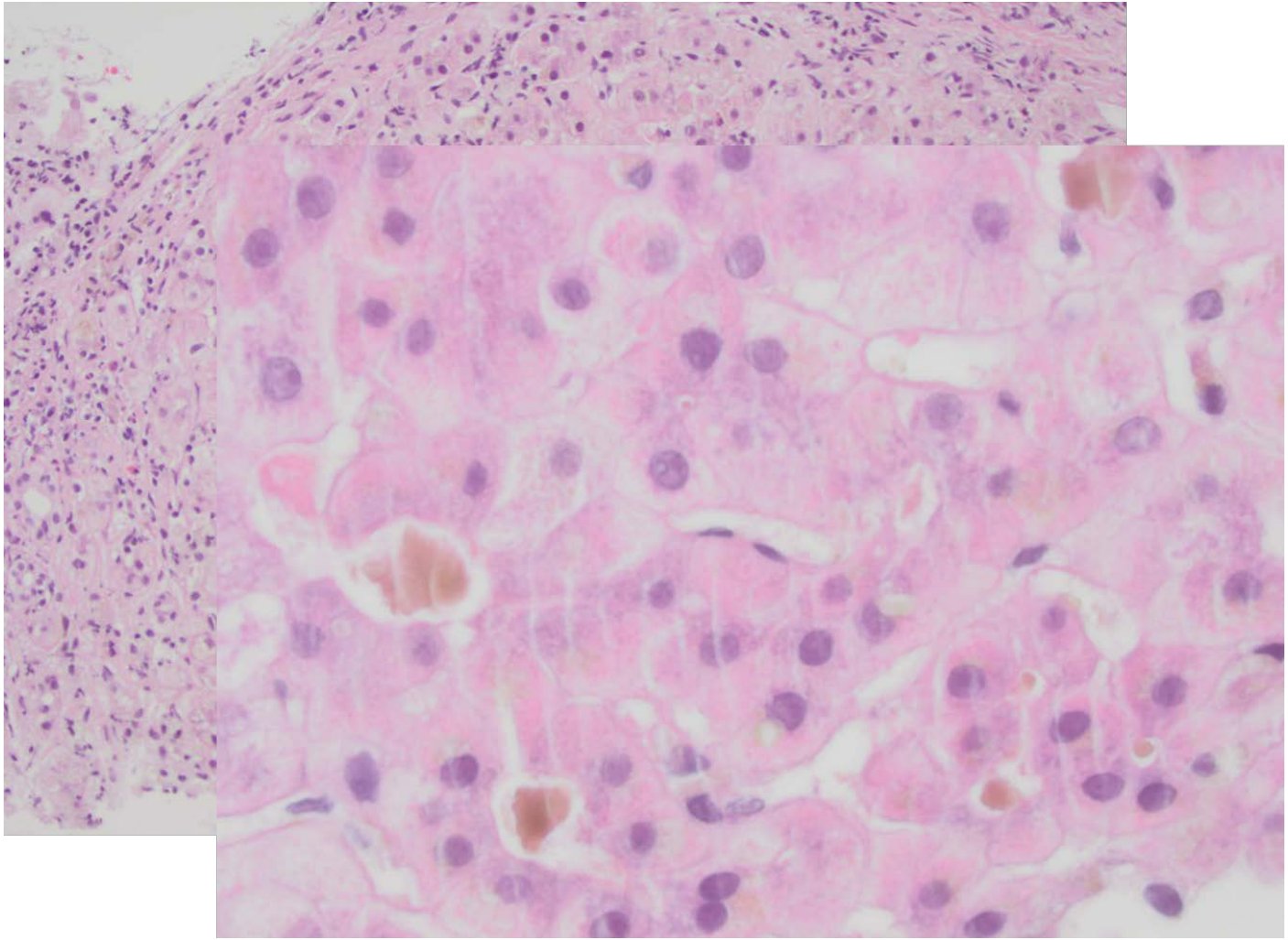
ASAT	266 U/L	CMV/ HSV -
ALAT	286 U/L	
Albumine	21 g/L	
INR	1.29	

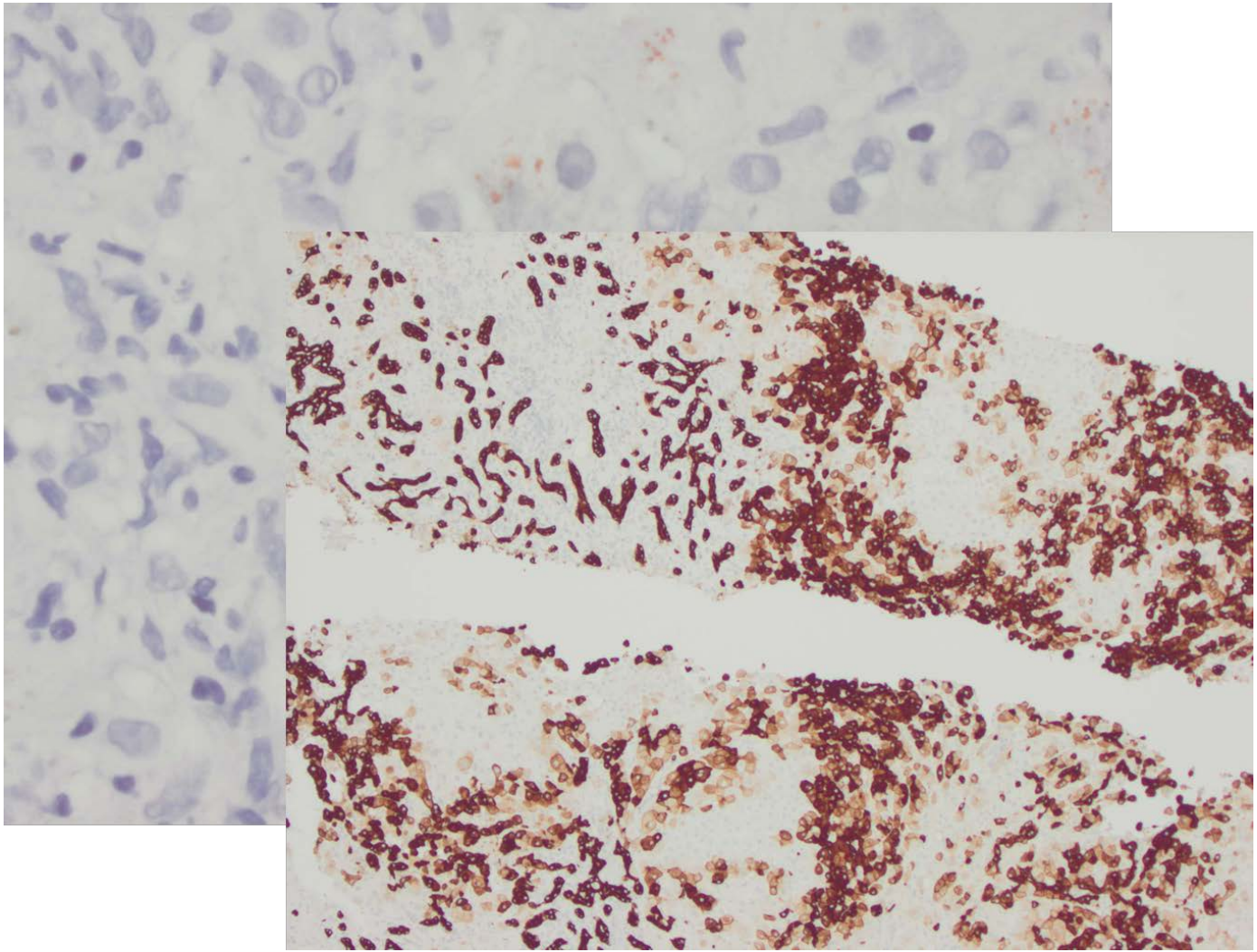
Onbegrepen cholestatische afwijkingen => leverbiopt

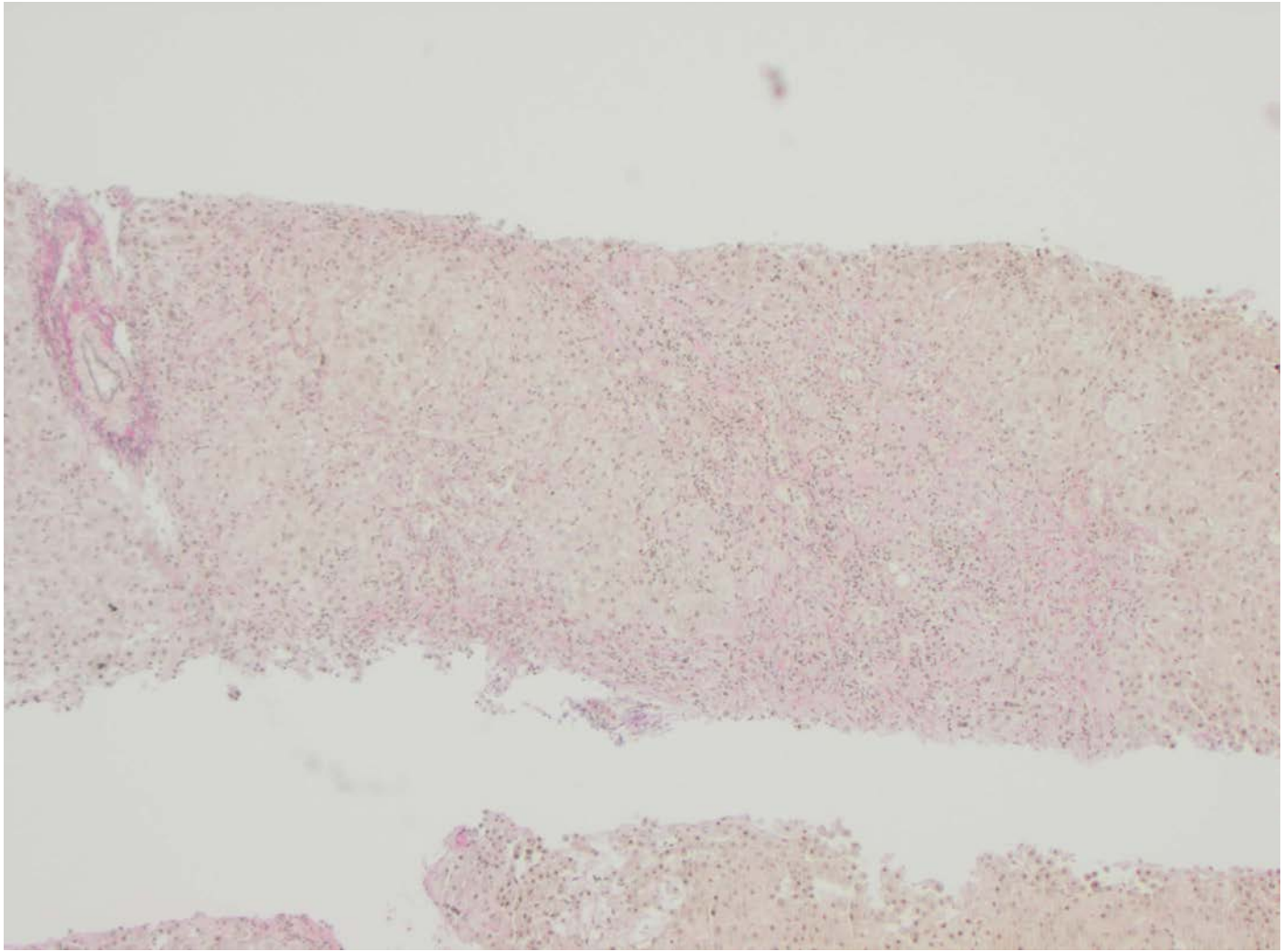
Pat W

T16-6847









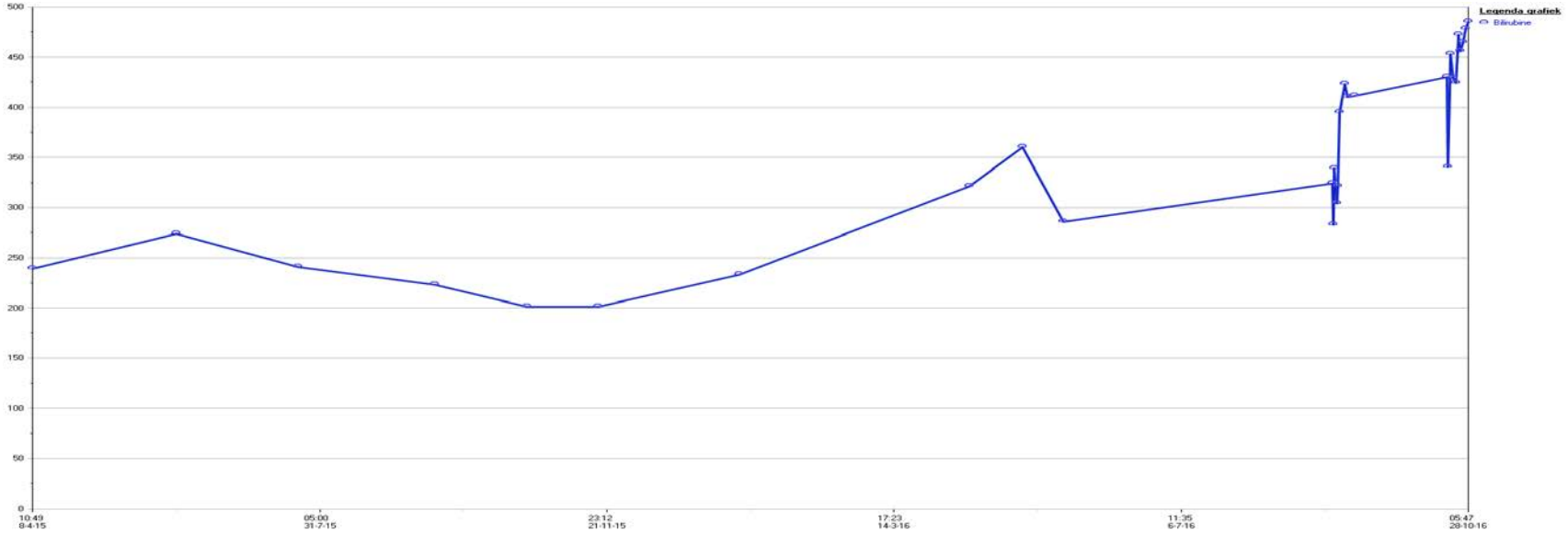
Leverbiopt: cholestatisch schadepatroon met bilirubinostase (gal) en tekenen van cholaatstasis (rententie galzouten)

~ toxische origine, in dit geval bij antibioticagebruik

Er is hooguit **recente fibrose**

Beloop

64 jarige patiënt met cholestatische levertestafwijkingen op basis van flucloxacilline, gestart met ursochol => vanishing bile duct syndrome

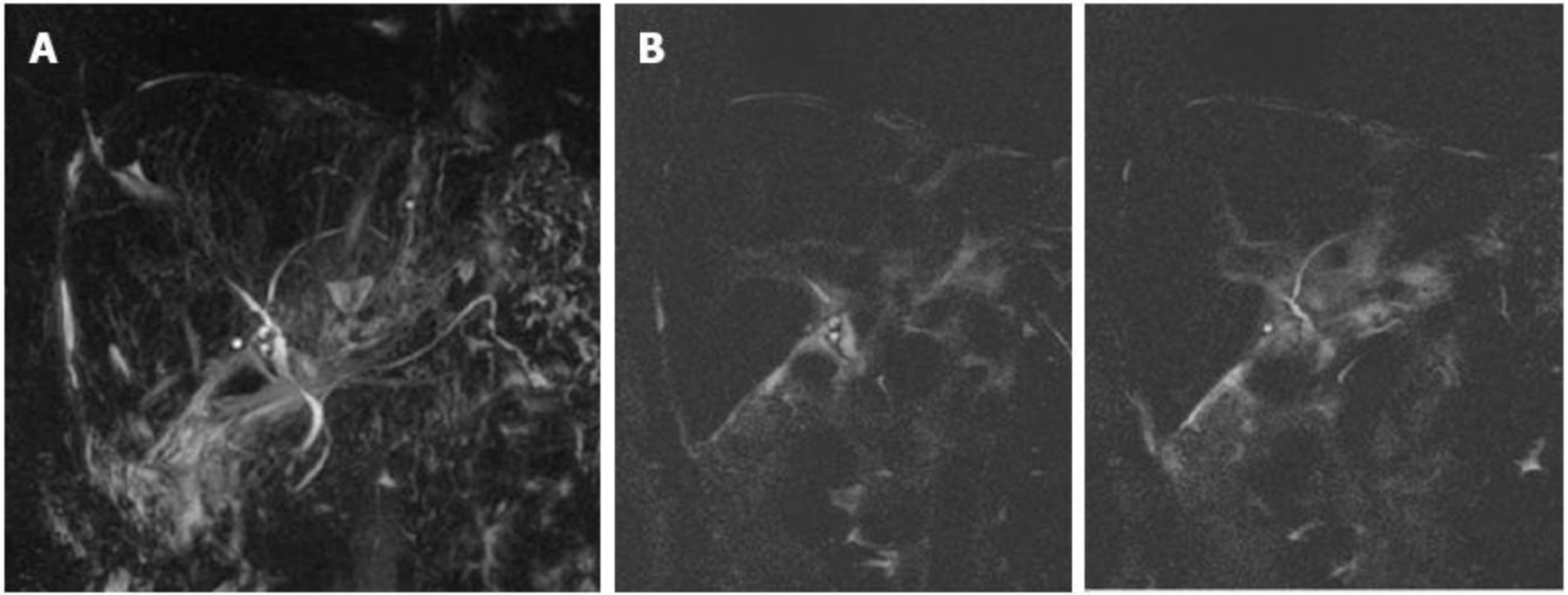


Flucloxacilline & DILI

- Mild verloop met lichte transaminasen stijging,
- Cholestatische levertestafwijkingen
- Onset toxiciteit: 1- 6 weken
- Vanishing bile duct syndroom zeldzaam
  - persisterend verhoogd bilirubine en alkalische fosfatase >> 6 mnd
  - destructie van intrahepatische galwegen => jeuk, icterus
  - chronische leveraandoening: Ltx << 3 jaar
  - associatie met antibiotica

Davies et al. J Hepatology 1994;20:112
www.livertox.nih.gov

Vanishing bile duct syndroom



Boraschi et al. World J Gastroenterol. 2014; 20(32): 11080-11094

Drug induced liver injury

10% acute hepatitis

Presentatie >> asymptomatisch - icterus

Patroon
- hepatocellulaire schade
- cholestatische schade
- gemengd
- auto immuun fenomenen (ANA)

Causaliteit

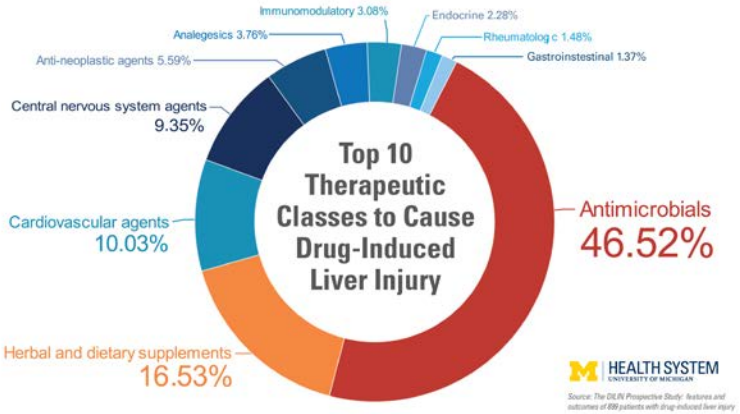


Table 2 Overview of drug-induced liver injury patterns

Histological pattern	Differential diagnosis	Common drugs involved
Acute hepatitis and cholestatic hepatitis	Viral hepatitis, autoimmune hepatitis, Wilson disease, idiopathic	See table 3
Acute liver failure		
Necrosis with marked inflammation	Autoimmune hepatitis, viral hepatitis, Wilson disease	Isoniazid, monoamine oxidase inhibitors, anticonvulsants (phenytoin, valproate), antimicrobials (sulfonamides, cotrimoxazole, ketoconazole)
Necrosis with little or no inflammation	Herpes simplex or adenoviral hepatitis, Wilson disease, malignant infiltration	Acetaminophen, cocaine, MDMA (ecstasy), carbon tetrachloride
Microvesicular steatosis with little or no inflammation	Acute alcohol intoxication, Reye syndrome, fatty liver of pregnancy	Tetracycline, nucleoside analogues
Chronic hepatitis		
Autoimmune marker-negative	Autoimmune hepatitis. chronic viral hepatitis, Wilson disease	Lisinopril, sulfonamides, trazodone, uracil, tegafur, tamoxifen, methotrexate
Drug-induced autoimmune hepatitis	Autoimmune hepatitis	Minocycline, nitrofurantoin, methyldopa, clometacin
Cholestasis		
Bland cholestasis	Sepsis, cardiac failure, shock, large duct obstruction, benign intrahepatic cholestasis, intrahepatic cholestasis of pregnancy	Anabolic/androgenic steroids, oestrogenic steroids, NSAIDs (nimesulide, piroxicam)
Cholestatic hepatitis (cholangiolitic or hypersensitivity cholestasis)	Viral hepatitis, large duct obstruction	Chlorpromazine, clarithromycin
Granulomatous hepatitis	Infections, sarcoidosis, primary biliary cirrhosis, talc, metal toxicity	Isoniazid, interferon, phenytoin, allopurinol (also see box 2)
Steatosis/steatohepatitis		
Macrovesicular steatosis	Diabetes, obesity, Wilson disease, hepatitis C	Alcohol, steroids, total parenteral nutrition, gold, chlorinated hydrocarbons, chemotherapeutic agents (5-fluorouracil)
Microvesicular steatosis	Fatty liver of pregnancy, carnitine deficiency, Reye syndrome	Cocaine, tetracycline, valproic acid, zidovudine
Steatohepatitis	(See macrovesicular steatosis differential)	Amiodarone, chemotherapeutic agents (irinotecan), perhexiline
Vascular abnormalities		
Sinusoidal obstruction syndrome	Myeloablation, venous outflow obstruction, right heart disease	Oxaliplatin, pyrrolizidine alkaloids, chemotherapy for ALL

ALL, acute lymphoblastic leukaemia; MDMA, 3,4-methylenedioxymethylamphetamine; NSAID, non-steroidal anti-inflammatory drug.

Drug induced liver injury

Behandeling: staken medicatie

Medicamenteus in specifieke gevallen

- N-acetylcysteine
- L carnitine
- Corticosteroïden

Gunstig beloop -> 5-10% chronisch
(>> cholestatische schade)

SAMENGEVAT

Drug induced liver injury komt vaak voor

Klinisch en histologisch beeld variabel

Therapie: staken oorzakelijke agens, klein deel chronisch

Bij levertestafwijkingen: denk aan DILI!

www.livertox.nih.gov

Roussel Uclaf Causality Assessment Method (RUCAM)

Time of onset of the event	Type of liver injury				Score
	Hepatocellular		Cholestatic/mixed		
	1st treatment	2nd treatment	1st treatment	2nd treatment	
From drug intake until onset reaction	5-90 days	1-15 days	5-90 days	1-90 days	+2
From drug withdrawal until onset reaction	<5 or >90 days	>15 days	<5 or >90 days	> 90 days	+1
	< or =15 days	< or =15 days	< or =30 days	< or = 30 days	+1
Course of the reaction	Difference between peak ALT and ULN value		Difference between peak ALP (or bilirubin) and UNL		
	>50% improvement at 8 days				+3
	>50% improvement at 30 days		>50% improvement at 180 days		+2
			<50% improvement at 180 days		+1
	Lack of information or not improvement				0
	Worsen or <50% improvement at 30 days				-1
Risk factors	Alcohol		Alcohol or pregnancy		+1
	Age > or =55-years old		Age > or = 55-years old		+1
Concomitant therapy	None: 0, drug with suggestive timing: -1, known hepatotoxin with suggestive timing: -2, drug with other evidence for a role: -3				
Exclusion of non-drug related causes	HAV, HBV, HCV (acute), biliary obstruction, alcoholism, recent hypotension (shock liver), CMV, EBV, and herpes virus infection.				-3 to 2
Previous information on hepatotoxicity	Reaction in product label: +2, reaction published; no label: +1, reaction unknown: 0				
Rechallenge	Positive: +3, compatible: +1, negative: -2, not done or not interpretable: 0				
Results >8 points, definite; 6-8 points, probable; 3-5 points, possible; 1-2 points, unlikely; <0 points excluded					

ALT, alanine aminotransferase; UNL, upper normal limit; ALP, alkaline phosphatase.