Case Report - Histological Findings and Algorithm for Morphological Differential Diagnosis in Drug-induced liver injury

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Clinical data are delivered by the clinician Georgi Chaltikyan, MD, PhD and are reported on the bottom of this abstract.

We received tissue of liver biopsy of a 6 year old girl. The score biopsy measured 6 mm in length and contained 6 portal tracts. According to guidelines for diagnosing liver diseases a liver biopsy should contain at least 6-8 portal tracts and should be at least 15-30 mm long. It is a fact that pathologists are unable to interpret histologic alterations of liver tissue sufficiently without knowledge of all clinical and laboratory data. In so far firstly the suggestive diagnosis was a descriptive one (26/05/2011): chronic active hepatitis with interface hepatitis and hydropic liver cell injury - differential diagnosis: autoimmune hepatitis versus drug-induced liver cell injury has to be discussed (if supplied liver tissue is representative). Sufficient laboratory and clinical data were supplied to the pathologist on 25/08/2011.

In general histologic changes in the liver tissue can be highly variable: minimal or severe changes in portal tracts or intralobular. Similarity to non-alcoholic steatohepatitis**,** autoimmune hepatitis**,** acute and chronic inflammation of the liver**,** cholestasis**,** acute liver failure and cirrhosis

The small liver biopsy delivered following features :

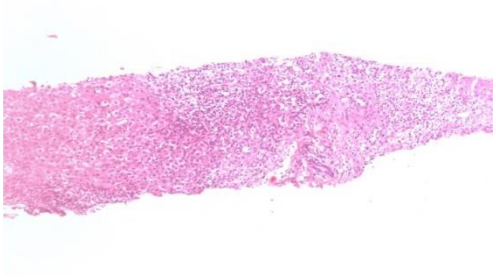

Figure: high inflammatory activity by dense infiltration with predominantly mononuclear inflammatory cells

The total of clinical, biochemistry, laboratory and histological findings are consistent with drug-induced liver injury.

See also Powerpoint presentations: Medikamentös-toxische Leberschädigungen and Drug-induced liver cell injury Case report AK 7.7.05

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Clinical Data:

ARABKIR
JOINT MEDICAL CENTRE
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ԲԺՇԿԱԿԱՆ ՀԱՄԱԼԻՐ

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Name: K.A.

DOB: 07.07.2005.

Admitted: 23.03.2011

Diagnosis: main – Total autoimmune alopecia,

Concomitant – Toxic hepatitis (?).

Presenting complaint: alopecia, icteric coloration of the skin and sclerae, itching, urine hyperchromia, acholic stools, weakness, fatigue.

Past medical history: the child from the first normal pregnancy and delivery, breast feeding up to 6 mm old. History of measles and respiratory infections. Normal development. No trauma or surgery history. No allergies.

History of present illness: Since 2009 the child developed first focal, than total alopecia, shedding of the scalp hair, eyebrows, eyelashes, thickening and yellowish discoloration of the toe nails. The child had multiple dermatology consults. After failing multiple treatment regimens (vitamins, anthelmintics, homeopathic therapy, local applications) the patient was consulted at Schneider Children Hospital in Israel in June 2010. She was diagnosed Autoimmune Alopecia, and prescribed pulse therapy with Solu-Medrol (180 mg/day x 3 days of each month). Starting in July 2010 the child received 6 courses of Solu-Medrol therapy at “Arabkir” MC.

Course 1 - 10.07 – 23.07.10

Course 2 - 19.08 – 23.08.10

Course 3 - 22.09 – 24.09.10

Course 4 - 25.10 – 28.10.10

Course 5 - 07.12 – 10.12.10

Course 6 - 22.02 – 03.03.11

However, as became evident recently, the child since September 2009 had concomitantly been given local applications of Rubia tinctorum L., with mayonnaise and in a combined preparation, twice a week, upon recommendation of a local pharmacist.

As a result of the above treatment the child had positive effect, the scalp hair, nails, eyebrows and eyelashes partially recovered.

Starting from the 4th Solu-Medrol course she developed hepatic cytolysis accompanied by intrahepatic cholestasis, manifested by elevated serum transaminases, bilirubin, as well as serum GGT and alkaline phosphatase. [Pl see the chemistry profiles below]

Physical examination upon admission: The child is generally feeling well, with no acute distress. The skin and sclerae are moderately icteric, no rash is noted, solitary telangiectasias on the buccal skin (present also in her mother and grandmother). Focal hair growth on the head. Peripheral lymph nodes not enlarged, mobile, painless. Musculo-skeletal system unremarkable. Lungs clear. Heart sounds loud, rhythmic, HR 112 beat/min, mild systolic murmur along the left sterna margin maximal at the 5th point. Tongue wet, with yellowish-whitish charge. Abdomen soft, non tender. Liver +2 under the costal margin, firm. Spleen not palpable. Stool once daily, normal consistency. Urinary output normal.

Summary of lab. data preformed at "Arabkir" MC

Complete blood count

	Course 1	**Course 2**	**Course 3**	**Course 4**	**Course 5**	**Course 6**		
	19.07.10	19.08.10	22.09.10	25.10.10	07.12.10	22.02.11	05.04.11	Normal values
Hb	129	128	131	133	137	137	127	120 – 140g/L
RBC	4.3	4.3	4.36	4.43	4.56	4.56	4,4	3.9 – 4.7x10^{12}/L
Fi	0.9		0.9	0.9		0.9	0,86	0.85 – 1.05
Ht	38		37	39		38	37	36 - 46%
Reticulocytes								2 – 14 ‰
Platelets	320	300	317	310	281	286	314	150-400x10^{9}/L
WBC	13.7	8.4	10.5	10.7	10.7	11.4	9	4.0-10x10^{9}/L
Bands	4	2	4	2	2	2	1	1-6%
PMN	64	25	50	54	48	41	35	47-72%
Eos	1	7	2	1	2	2	2	0.5-5%
Bas								0-1%
Lym	23	54	36	35	36	47	52	19-37%

Mon	6	12	8	8	12	8	10	3-11%
ESR	11	12	5	9	5	5	6	2-10 mm/h

Serum chemistry panel

	Course 1	**Course 2**	**Course 3**	**Course 4**	**Course 5**	**Course 6**	-	-	-		
	19.07.10	19.08.10	22.09.10	25.10.10	07.12.10	22.02.11	28.02.11	23.03.11	26.03.11	05.04.11	Normal
Total protein	83	67.7	71	69	74	71		64		78	51-75 g/L
Urea	3.4	2.6	3.2	4.2	2.6	3.4		2.2			<8.3 mmol/L
Creatinine	26	35			24	27		25		27	15-68 mmol/L
Na	139			136		138		143		138	135-150 mmol/L
K	4.3			4.3		4.4		4.1		4,2	3.8-5.1 mmol/L
Ca	1.15			1.08		1.16		1.21		1,11	1.13-1.32 mmol/L
P	1.65			1.79		1.77		1.26			1.1 – 2 mmol/L
Glucose		5.2	4.2			3.8	4.3	4.3		4,2	2.8-5.5 mmol/L
Bilirubin TOTAL	**21.8**			**14.6**	**19.5**	**38.8**	**31.3**	**120**	**77**	**77,7**	<17 mcmol/L
Bilirubin DIRECT	**3.3**			**2.6**		**23.3**	**17.3**	**85**	**55**	**70,6**	0-3.4 mcmol/L
Bilirubin INDIRECT	**18.5**			**12**		**15.5**	**14**	**35**	**22**	7,1	<13.6 mcmol/L
Albumin	43 g/L	43 g/L				68.1%		67.2%		42,6%	52-65% 28-45 g/L
α1						3.4		6.9			2.5-5%
α2						9.8		5.2			7-12%
β						11.9		8.6			8-14%
γ						6.8		12.1			12-22%
Amylase						61		44.3		59	28-100

ALT	16	22	26	39	**212**	**372**	**516**	**562**		**794**	10-50
AST	30	36	38	44	**115**	**404**	**500**	**610**		**1009**	<38
GGT				8.2		**80**		**91**	**81**	**161**	8-61
AP				156		**283**		**349**	**308**	**432**	<200
Cholesterole							4.0		4.4		<5.2 mmol/L
LDL							2.5		2.5	3,11	2.59-3.34 mmol/L
Tryglycerides							0.7				<2.3 mmol/L
CRP	-	-	-	-	-	-			-	+	-

Clotting panel

22.07.10

Clotting time Lea-White: 7 min (5-10 min), prothrombine index 83% (80-105%), thrombotest ITA IV (IV-V), plasma heparin tolerance 9 min (6-13 min), fibrinogen A 2.86 g/L (2-4 g/L), fibrinogen B (-).

05.04.11

Clotting time Lea-White: 7 min (5-10 min), prothrombine index 76% (80-105%), thrombotest ITA IV (IV-V), plasma heparin tolerance 10.5 min (6-13 min), fibrinogen A 2.6 g/L (2-4 g/L), fibrinogen B (-). INR 1.5

19.07.10 – 11.08.10

ANA 12 U negative (N < 20)

dsDNA 125 negative (N 0-200 ME/ml)

20.07.10

Thyroid peroxidase AB (TP-ab): 11.1 (<50 U/ml)

02.08.10

C3 fraction compl 0.98 (0.84 – 1.67 g/L)

C4 fraction compl 0.2 (0.16 – 0.31 g/L)

19.07.10

HbsAg: negative

ASLO <200 (normal <200)

Tuberculosis, antibodies: negative

Brucellosis, antibodies: negative

24.02 – 03.03.11

ANA 11 neg (N < 20)

dsDNA 140 neg (N 0-200 U/ml)

24.02.11

HBsAg: neg (confirmed at two labs)

Anti-HBs-ab: 100 IU/l

HBcor-IgG: neg

HCV total ab: neg

IgM – EBV: neg

CMV IgG 5 U/ml (N <2 U/ml)

HSV 2 IgG 0.46 U/ml (N <0.9 U/ml)

HAV IgM: neg

EchoCG

19.07.10 Normal

24.02.11 mitral prolapse

ECG

19.08.10, 25.10.10, 25.02.11 sinus tachycardia 120/min

Abdominal ultrasound:

19.07.10 – normal

25.10.10 – minor hepatomegaly

24.02.11

Liver: right lobe mid-clavicular size 9.8 cm, antero-post size 7.6 cm, oblique size 10.67 cm, left lobe length 6 cm, hilar lymphnode 1.16 cm; echogenicity normal, increased density of **intrahepatic bile duct walls and vascular walls.** Portal vein 0.5 – 0.6 – 0.4 cm, wall 0.21 cm. Gallbladder normal, contour smooth, contains septum, content homogenous. Pancreas – topography normal, contour normal, structure homogenous, size head 1.07 cm, body 0.9 cm, tail 1.7 cm. Gastric and duodenal wall thickness is normal. Spleen 8.5 x 3.7 cm, homogenous.

Other organs unremarkable.

No ascites, no mesenteric adenopathy.

Conclusion: mild hepatomegaly.

25.03.11

Serum Cu: 0.236 g/L (N 0.18 – 0.45 g/L)

Urinary Cu: 56.4 mcg/L (N below 70)

Cerulloplasmin: 0.007 g/L (< 0.03 g/L)

PCR HSV - neg

PCR CMV – neg

IgG 1.167 g/L (N 3.5 - 14 g/L)

IgA 0.242 g/L (N 0.3 – 2.3 g/L)

IgM 0.179 g/L (N 0.4 – 1.5 g/L)

Consulted by a toxicologist, and diagnosed with “Toxic hepatitis”, received IV fluids; on April 5 started on high dose oral ACC (acetylcysteine). Condition remained stable despite elevated enzymes.

Further studies at Labor Limbach – Heidelberg:

Ceruloplasmin in Serum	**275** mg/l	260 - 460
Copper, total in serum	**1096** ug/l	800 - 1600
AAb to Mitochondrions (AMA)	**1: < 10**	1: < 10
AAB to Liver-Kidney Microsomes	**1: < 10**	1: < 10
AAb to Smooth Muscles (SMA)	**1: < 10**	1: < 10
Ab agaist sol. liver antigen	**< 2.0** E/ml	< 20
Hepatitis A Ab, IgM	**negative**	
HBs-Antigen	**negative**	
anti - HBc	**negative**	
Hepatitis C - Antibody	**negative**	

Epstein-Barr-VCA-IgM (serum)	**< 4** U/ml	< 13
Zytomegalie IgM Antikörper	**negative**	
AFP (Roche - ECLIA)	**396**kIU/l	< 5.8
Hepatitis-B-Virus-DNA in plasma (PCR)	**< 0.010** kIU/ml	
Hepatitis C-Virus-RNA in plasma (PCR)	**negative**	

IV contrast enhanced CAT performed did not reveal any mass lesion in the liver.

Liver biopsy: pattern consistent with DILI.

Clotting panel 18.04.11

Clotting time Lea-White: 9' 30'' (5-10 min), prothrombine index 75% (80-105%), thrombotest ITA V (IV-V), fibrinogen A 3.3 g/L (2-4 g/L), fibrinogen B negative (-). INR 1.54

Heptral IV infusion 200 mg/day started 15.04.2011

Chemistries began normalizing since late April-May, and continued thereafter. The patient was discharged on May 18th, and remained under outpatient control. Her subsequent course was almost uneventful apart from an acute febrile (up to 39°C) illness with diarrhea for 2-3 days, treated with Nurofen, Smecta and Rehydron.

She continued oral Heptral ½ caps b.d.t. for a total of 3 months (until end of July), and was also given Vit E and A for 20 days.

She currently feels well, is fully active, completely asymptomatic, and on no medication.

NB: Please refer for separate MS Excel spreadsheet for complete CBC and chemistry data.

Attending K.G. Mirzabekyan

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