Acute grade IV toxic hepatitis due to the e-cigarette

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Abstract

A 46-year-old woman presented at the emergency department because of acute hepatitis with jaundice. After hepatological work-up including liver biopsy, drug induced liver disease (DILI) was suspected. Patient recovered completely within a few months.

One year later she presented again with jaundice due to acute hepatitis. Vaping was the only agent that could be identified as causative agent for DILI. After VAPING cessation, the hepatitis resolved completely. Calculated RUCAM score was 10, making the diagnosis of toxic hepatitis very likely. During follow-up liver tests remained normal.

This is the first report of severe DILI secondary to the use of e-cigarettes. In future vaping can be included in the differential diagnosis of DILI. (Acta gastroenterol. belg., **2024,** 87, **44-47**).

Keywords: Case report, DILI, vaping, e-cigarette.

Introduction

DILI and Herb Induced Liver Injury (HILI) is caused by a variety of drugs, toxins, chemicals but also herbal and dietary supplements which can cause hepatoxicity. Worldwide estimated annual incidence of DILI is 19 per 100,000 persons exposed (1-3).

DILI can mimic a wide spectrum of acute and chronic hepatic diseases such as alcoholic and non-alcoholic steatohepatitis, viral or autoimmune hepatitis, metabolic diseases, even granulomatous and vascular disease (4,5). Therefore, the diagnosis of DILI relies on the exclusion of other etiologies of liver disease and thoroughly history taking.

Toxic hepatitis can be classified as hepatocellular, mixed or cholestatic. Hepatocellular hepatitis is characterized by predominant increase of alanine-transaminase (ALT), whereas in cholestatic hepatitis alkaline phosphatases (AP) are most elevated. Taking the upper limit of normal (ULN) of both parameters into account, an R-score can be calculated with following formula: R = ALT/ULN divided by AP/ULN (6). Hepatocellular hepatitis is characterized by an R above 5. Hepatitis is called cholestatic when R<2 and mixed with R between 2 and 5.

Severity of hepatitis can be determined using the criteria of Fontana (7). Hepatitis is classified as severe or Grade IV if hepatitis is complicated with organ failure, ascites, encephalopathy, if jaundice lasts more than 3 months or when ALT raises above 10*ULN or total bilirubin level (TBL) above 5 mg/dl. Hepatocellular DILI with accompanying jaundice has a troublesome prognosis (8). According to New Hy's law TBL > 2.5*ULN and R ratio > 5 have a bad prognosis (9). Drug re-challenge is clearly discouraged, since it can provoke more serious liver disease, but if performed it adds diagnostic value.

Last decade, "vaping" or the e-cigarette is gaining popularity. In 2020 in Europe, the prevalence of using e-cigarettes is 26% lifetime, 14% are current users. Vaping is observed in people who try to quit smoking, in combination with current smoking and as an "innocent" initiation to smoking in adolescents (10). Adverse events of smoking cigarettes are recognized among the public, but less is known about possible pulmonary and hepatotoxic effects of "vaping" (11). Fan et al. published a report of vaping as a possible cause of toxic hepatitis (12).

Case Report

A female patient, °1972 with a history of a gastric bypass in 2014 presented at the emergency department on April 23th 2018 with a 2 month history of progressive asthenia, epigastric tenderness and jaundice. She was on ethinylestradiol/levonorgestrel and pantoprazole and used e-cigarettes. She had no recent weight loss, alcohol consumption or viral symptoms. We refer to Table 1 for biochemical results. TBL was 9.3 mg/dL. Values for liver tests expressed in U/l are 1018 for AST (aspartate transaminases**)**, 1432 for ALT, 196 for AP and 144 for gamma glutamyl transferases. An extensive viral, auto-immune and metabolic work-up was completely negative. Serology for Toxoplasma, HIV, syphilis and viral hepatitis A, B, C and E was negative. Smooth-muscle-antibodies, liver-kidney-microsomal-antibodies, anti-mitochondrial-antibodies, anti-nuclear-antibodies and ANCA were all negative. She had normal immunoglobulin levels.

On abdominal ultrasound only hepatosplenomegaly was found.

Liver biopsy showed cholestatic hepatitis with severe lobular necroinflammation. The inflammatory infiltrate predominantly consisted of lymphocytes with few eosinophils, but no significant plasma cell-component. There

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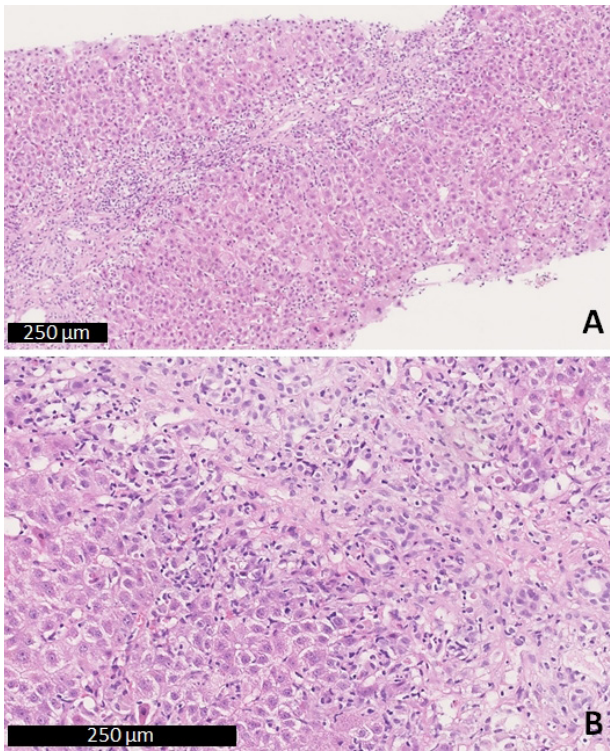

Figure 1. — A: Liver biopsy shows cholestatic hepatitis with severe lobular necroinflammation, severe interface hepatitis with bridging necrosis. Mild ductular reaction is observed, but no ductal injury; B: Higher magnification: The inflammatory infiltrate predominantly consists of lymphocytes with few eosinophils, but no significant plasma cell-component.

was severe interface hepatitis with signs suggestive of bridging necrosis. Preferential diagnosis on liver biopsy was DILI, autoimmune or viral hepatitis. There were no arguments for benign recurrent intrahepatic cholestasis (Figure 1). No other examinations were performed.

The diagnosis of DILI was assumed. Already during the admission of 6 days patient started to recover. She became free of complaints the following months. Liver tests and ultrasound normalized (Table 1).

However, 1.5 years later, November 13th of 2019, she again presented at the emergency room in another hospital because of progressive jaundice, nausea, itching and abdominal discomfort. TBL was 14.4 mg/dl, AST 847 U/l, AP 170 U/l. Again, biochemical and serological exploration and abdominal ultrasound could not demonstrate a cause for the acute hepatitis (Table 1). There was no intake of known hepatotoxins, but the patient mentioned that she started vaping three months prior to the first hospitalization and stopped upon first admission. She restarted vaping a month prior to the second hospitalization. She was vaping fluid with nicotine concentration of 3 mg/ml of the company Flavourtec (flavours raspberry and cappuccino) and the company American Stars (flavours honey hornet and Jamaican fruit). Usually, a unit of vaping consists of 1 ml of fluid. After cessation of vaping following the second admission, a complete recovery was observed again (Table 1).

The RUCAM score for the patient was calculated on table 2, resulting in a score of 10, making the diagnosis of DILI highly probable (13). On repetitive blood analysis, the last taken at March 2nd 2022, all liver tests remained normal.

The toxic hepatitis should be classified as hepatocellular since she had an R score of 16 (ALT 24*ULN, AP 1.5*ULN: 24/1.5=16) (6).

Her ALT raised till 24*ULN, TBL was 14 mg/d. Both values are clearly above the level required to diagnose a toxic hepatitis grade IV (see introduction) (7).

The TBL above 2.5*ULN and the R score above 5 gave her a 10-50% chance of dying or need for liver transplantation (OTLX), according to new Hy's law (6,7). Fortunately, following cessation of VAPING she recovered twice without sequelae.

Discussion

DILI is a diagnosis of exclusion since specific biomarkers are still lacking (4,5). The RUCAM score helps to confirm the diagnosis (13). RUCAM points to

Table 1. — **Laboratory investigations and evolution**

Labo	23/1/18	23/4/18	8/6/19	11/12/18	11/9/19	13/11/19	29/11/19	31/1/20
Vaping	start	stop	no	no	start	stop	no	no
Eo's		5,2%	5%	6,7%		6,5%	3,2%	3,2%
AST (U/l)		917	30	11		846	43	19
ALT (U/l)		1448	35	9		1022	66	22
AP (U/l)		167	137			170	143	72
GGT		125	65	12		144	68	18
TBL		9,32	3,5	0,45		14,4	4,4	0,7
INR		1,49	1,0			1,0	1,0	1,0
Alb		20		41		34	40	42
Bile-acid (mmol/l)						411		11

Eo's: eosinophils, AST: Aspartaat-Amino-Transferase. GGT: gamma glutamyl transfererases; TBL: total bilirubin level in mg/dl. INR: internationalized normalization ratio. Alb: albumin in g/l.

Table 2. — **RUCAM score**

Type of liver injury	Cholestatic/mixed	Patient's score
1. Time of onset of the event	First exposure	
Time from drug intake until reaction onset	5 to 90 days	+2
Time from drug withdrawal until reaction onset	≤30 days	+1
2. Alcohol or pregnancy risk factor	Absent	0
Age risk factor	<55 years	0
3. Course of the reaction	≥50% improvement 180 d	+2
4. Concomitant therapy	Time to onset incompatible	0
5. Exclusion of non drug-related causes	Rule out	+2
6. Previous information on hepatotoxicity	Reaction unknown	0
7. Response to re-administration	Positive	+3
Total score		+10

distinct domains such as temporal relationship between exposure to a particular drug and liver injury (both its onset and course), exclusion of alternative non-drug-related etiologies, exposure to other medications that could explain DILI, risk factors for the adverse hepatic reaction, evidence in the literature regarding DILI from the drug in question and response to re-exposure to the toxin. The RUCAM score can range from -9 to +10. According to this score DILI can be graded as highly probable (score > 8), probable (6-8), possible (3-5), unlikely (1-2), or excluded (≤0)) (9). In the current case, the unplanned re-exposition helped for the definitive diagnosis (2). The persistent normal liver set following avoidance of VAPING further confirmed the hypothesis.

Treatment of DILI consists of withdrawal of the causal agent. Prognosis of DILI is worrisome when hepatocellular hepatitis is complicated with cholestasis (8). Our patient had a 10-50% chance of evolution to terminal liver failure (6), requiring OTLX in some cases (14). Up to 15 % of liver transplantations are performed for patients with acute liver failure secondary to DILI. Fortunately, our patient recovered completely twice following vaping cessation.

Most known hepatotoxic agents responsible for DILI are registered and a complete list can be consulted on http://livertox.nih.gov (15). Currently, VAPING is not included as a causative agent for DILI. The e-cigarette exposes to less tar as regular smoking but exposes to chemicals as propylene glycol, glycerol, nicotine (0-50 mg/ml), and polycyclic aroma's (5%), nitrosamines, phenols and heavy metals. Vaping can induce hepatic steatosis, oxidative stress, hepatocyte apoptosis and liver function abnormalities (10,11). The exact bio-chemical composition of the fluid used by our patient is not mentioned in the prescription of the products. The composition cannot be detected by a quest on the internet and was not provided by the company on our request. As such, the exact causative agent in the e-cigarettes cannot be defined in the current case. Additional basic research is needed to further elucidate possible toxic mechanisms.

In this article, we describe for the first time a case with acute relapsing grade IV toxic hepatitis due to "vaping" or the e-cigarette. The diagnosis in this patient could only be made by careful history taking, stressing the importance of the latter.

We believe that "vaping" must be included in the list of potential causes of patients presenting with DILI.

Conflicts of interest

No conflicts of interest.

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