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HEPATITIS TOXICA – CASE REPORT

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Toxic lesion of the liver is frequently a subject of differential diagnosis analysis of infectologists-hepatologists. The problem is being greatly increased by prescribed medicaments use and during self-treatment practice.

Liver damage mostly goes as cholestatic form of disease, with clinical manifestations of icterus, pruritus, changes of urine and stool color. Clinical finding is followed by characteristic laboratory findings (bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, cholesterol). In order to make complete diagnostic of these patients, it is often necessary to perform a liver biopsy and pathohistological examination of liver tissue. A 42-year-old female patient with cholestatic elements was examined, and the liver biopsy was performed after her clinical and laboratory examinations, when the toxic character of liver damage was confirmed. Acta Medica Medianae 2009;48(2):49-51.

Key words: *toxic hepatitis, medicaments*

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Introduction

As a central organ of the human organism the liver has multiple functions, including metabolism of different substances as well as medicaments. Medicaments are taken into the human organism, either on physician's recommendation or as self-treatment practice. Different lesions of the liver may occur during drugs intakes as a consequence of an irregular dosing or individual idiosyncrasy (1-5). More precisely, liver damage develops as a direct hepatotoxic injury of hepatocytes, trough hepato-sensitisation or by the both mechanisms together. Hepatitis medicamentosa is a rare condition, it is present in 1-3% of patients with hepatitis, while up to 30% of all fulminant hepatitides are accounted for drug caused lesions (2, 6). Essentially, an effect of psychopharmaceutical drugs influence on cytokines production, the major humoral mediators of inflammation and infection (7). Proinfective cytokines, tumor necrosis factor-alpha, interleukin beta 1 and interleukin 6 are released by kupffer cells or activated neutrophils and macrophages, they initiate hepatic cells defense mechanism, including activation of apoptosis. Reactive oxygen and nitrogen forms, generated in the response to cytokine induced stress signals in the liver parenchyma and by kupffer and inflammatory cells, mobilize the cells defense mechanism (inflammatory response and neutrophils infiltration) (8). Drug-induced liver damage develops during a treatment with large number of medicaments or when the treatment course is repeated. It can be acute or chronic depending on the liver damage duration (3). Large number of drugs may cause liver damage. Drug-induced liver damage may be asymptomatic or with maculopapular rash, itching, fever, chills, nausea, vomiting, loss of appetite, jaundice, dark urine, acholic stools, gingivorrhagia, hepatomegaly, pain under the right costal arch, diarrhea, abdominal pain, spider naevi and abdominal free fluid (9). Drug-induced liver damage is followed by increased levels of bilirubin, ALP, gamma GT, cholesterol, aminotransferases and eosinophils (2). Pathohistological examinations show focal necrosis of hepatocytes, cholestasis, periportal mononuclear and eosinophil cells infiltration (3). Hepatitis medicamentosa ends with a recovery, although it may progress into a chronic hepatitis or an acute liver failure with a lethal outcome (2). Hepatitis caused by medicaments is diagnosed with anamnestic data of drugs intake, clinical examination, laboratory findings, and not rarely, with a pathohistological confirmation. Therapeutic approach is based on an intake cessation of medicament that caused damage, and also on a substitutional and symptomatic therapy.

The aims of the study

The aims of this study were to clearly highlight the possible role and position of medicaments leading to a damage of the liver as a central organ of the human body, forms of its clinical manifestations, the liver dysfunction after an use of different medicaments (antidepressants, analgesics) and to review differential diagnostic difficulties in a clinician's work with these patients.

Case presentation

A female patient P.Z. was born in 1966. She works as a laborer and was hospitalized on 13th of May 2008.

Among her complaints dominant were: nausea, dull pain under the right rib arch, fatigue, dark urine, yellowish staining of skin and mucousas and itching all over the body. Between 02. and 13. of May 2008. the patient was hospitalized in the Health center in Vranje with a diagnosis of Hepatitis virosa acuta.

After her laboratorical and clinical findings got worse, together with negative results for viral hepatitis A or B infection, with a clinic's doctor approval, she was transferred to the Clinic for

infectious diseases with a diagnosis of Hepatitis toxica cholestasis in obs.

The anamnestic data show that since 2nd of April patient was under the treatment for: neurotic reactions (anxious-subdepressive type), *hemiparesis lat. dex. disc. inverterata, artralgia artic. Temporomandibularis bil., neuralgia n. trigemini sec., Sy. cervicobrachialis et cervicobasilaris, Discarthrosis C3-C4, c5-C6, C6-C7 susp., Neuralgia n. intercostalis bil. pp. lat. sin., Kyphoscoliosis thorac. alias, Lumboischiagia bil. pp. lat. dex. sympt., Dyscarthrosis L3-L4, L4-L5, L5-S1 susp., hypertensio artrerialis non fixata, gastritis chronica hyperacida, myalagia m. recti abdominalis bil.*

Because of these diagnoses patent was treated in private surgery for neurology and general medicine, with the following therapy: Maprotilin tab. à 25 3x1, Largactil tab. à 25, 1+1+2 schedule, Rivotril tab. 2 mg 1 in the evening, Flugalin tab. à 50 3x1, amp. Impletola 5,0cc (infiltrative), together with hygienic and dietary regimens and strict bed rest.

On the admission the patient was conscious, oriented, afebrile, average osteomuscular body build, skin and mucosas were intensively yellow. The liver was palpable at the right costal arch. Laboratory tests were immediately performed the next day (13.05.08), and these were the results: WBC 10.1, ne 57.9%, ly 30.6%, mo 6.6%, eo 4%, ba 0.9%, RBC 3.42, HGB 108, HCT 33, PLT 449, SE 46, AST 549, ALT 898, direct bilirubin 218, total bilirubin 102.4, ALP 518, cholesterol 21, gamma GT 642.9, triglycerides 2.62, alpha FP 3.34, fibrinogen 7.02, ANA, AGMA, ATA and AMA were negative, PTV 114%, aPTT 29, T3 0.88, T4 63.85, TSH 3.126. Upper abdomen ultrasound shows the normal liver position and size, with a slightly increased ehogenicity, with no focal lesions. Gall-bladder is without pathological findings. Bile ducts are not visible. The spleen is normal in size and homogenous.

Both kidneys have signs of microlithiasis without an obstruction. On May 19th, laboratory findings were following: Se 62, WBC 15.4, ne 64.9%, ly 23.6%, mo 0,75%, RBC 3.53, HGB 114, HCT 0.343, PLT 651, direct bilirubin 38.8, total bil. 88.5, ALP 586, gamma GT 824, proteins 70.3, albumins 39.4.

On May 23rd results were: AST 169, ALT 624, direct bil. 28.8, total bil. 69.4, LDH 508.5, ALP 542, gamma GT 908.5, cholesterol 16.37, ldl 12.34, hdl 2.36, triglycerides 3.43, proteins 69, albumins 40.3, LE cells 0, Fe 15.9. An ophthalmologist excluded existence of Keiser-Fleisher ring: Cu 25.98, ceruloplazmin 400.9, HBsAg neg., fibrinogen 5, CRP 5.8, CK 2.6.

On 24th of May, the patient was sent to a gastroenterologist and hematologist. The gastro-enterologist confirmed our working diagnosis - *cholestasis, hepatitis tox. PBC susp.* He suggested that ERCP or MRCP should be performed. At the same time, the hematologist gave his diagnosis: *hepatopathia, PBC and trombocytaemia*.

For now, there are no indications for an idiopathic thrombocytosis and the causes of secondary thrombocytosis should be excluded. Immune complexes were negative on 26th of May. On May 28th, the patient's analyses were repeated: se 54, wbc 8.4, ne 52.84, ly. 29.9, eo 6.3, mo 9.5, rbc 3.68, hgb 119, hct 35.8, plt 442, ast 294, alt 831, bil. dir. 20.6, total bil. 49, ALP 438, cholesterol 9.8, ldl 2.08, hdl 6.86, ldh 686, proteins 70.5, albumins 40.4, PTV 86%, aPTT 30", TV 17", FK I 782. On 6th June, a punctional biopsy of the liver was performed, when the diagnosis of *cholestasis, lesio hepatitis toxica* was established. The morphological finding of the biopsy indicated a cholestatic type of toxic liver damage.

During the hospitalization, patient underwent an intensive medicament treatment with corticosteroids, vitamin K, fluids, choleretics, ranisan, aspirin, lentostamin, kardiopirin, along with constant biohumoral monitoring. Patient was released home after 25 days, with a suggestion to continue the therapy with: Ursosan 3x2, Oligovit 2x1 and diet that Clinic for dietetic of the Public health institute recommended.

Six months after the discharge the patient had following laboratory results: WBC 10.7 G/L, ly 2.7 G/L, mid 0.6 G/L, gr 7.4 G/L, RBC 4.19 T/L, Hgb 131 mg%, Hct 377, PLT 321 G/L, AST 37 UI/L, Alt 38 UI/L, bil. 6.3 mmol/l, Alp 118 UI/L, gamma GT 68 UI/L, cholesterol 5.83 mmol/l, triglycerides 2.06 mmol/l, alpha-fetoprotein 3.44. Subjectively, the patient still feels some discomfort under the right rib arch and occasional abdominal distensions. Upper abdominal ultrasound is not showing any pathological finding, except the nephrolitiasis with no urine stasis.

Discussion

The patient P.Z. was treated for her neuropsychiatric difficulties by the neuropsychiatrist. On the basis of the clinical examination the patient underwent the treatment in intention to achieve rehabilitation. Polymorphism of the clinical problems has probably affected a variety and a number of recommended medicaments. Prescribed medicaments had antidepressive and analgesic action. During and after the course of treatment, the patient developed clinical manifestations of an acute liver damage. Among registered problems dominant were dyspeptic syndrome, icterus, pruritus and other. This clinical finding was also described by other authors, in which patients used similar or different drugs (4,5,7,10). Type of liver damage in these patients may be cholestatic, hepatotoxic or mixed (1,2,4,5). Our patient had a mixed type of liver damage (icterus, dark urine, hypocholic stool, pruritus). This finding had laboratorical confirmation, when the elevated values of bilirubin, cholesterol, alkaline phosphatase, glutamil transpeptidase, triglycerides were found, as well as significant elevation of amino-transferase level. Similar finding was noted by other authors in their reviews (3,6,11,12). The observed clinical-biochemical presentation makes a clinician wonder if there is a possibility of liver damage by some other agents (infective, immunological, malignant or other). In that order, further examinations were performed, with the objective to eliminate the suggested etiological factors of liver damage (12,13). Due to the intensive cholestasis, medical preparations were administered to lower the level of cholestatic enzymes on the one hand and concomitant clinical problems on the other.

Beside that, due to the initial inadequate therapeutic response, an aspiration liver biopsy was preformed and the obtained pathohistological finding confirmed a drug-induced liver damage. Further laboratory monitoring of the patient provide no elements that would indicate on a chronic evolution of the liver damage, as it is described by other researchers (10,12,14,15). The disease had prolonged course with a tendency of settling down. At the same time, during the hospital treatment of the patient, parameters that would indicate on a serious hepatocytes insufficiency or even a sign of an unfavorable disease progression were not observed, as other authors describe in similar situations (11,15).

Conclusion

1. A treatment with various medicaments carries a risk of liver damage, that may be different in type.
2. The most frequent type of liver damage is mixed type, which is also considered in differentional diagnosis of immunological, infectious and other diseases.
3. Pathohistological examination of affected liver represents the most reliable diagnostic procedure in resolving diagnostic dilemmas.
4. Anamnestic data of previous drugs intake are very important, because they can represent an inevitable etiological factor of developed disorders.

References

1. Kukavica D. Antituberculotic-induced liver dysfunction. Pneumon 2004; 41: 59-63.
2. González Galilea A, García Sánchez MV, la Mata García M, Miño Fugarolas G. Early-onset acute toxic hepatitis induced by intravenous amiodarone administration. Gastroenterol Hepatol 2002; 25(6): 392-4.
3. Andrade RJ, Lucena MI, Fernández MC, Vega JL, García-Cortés M, Casado M, et al. Cholestatic hepatitis related to use of irbesartan: a case report and a literature review of angiotensin II antagonistassociated hepatotoxicity. Eur J Gastroenterol Hepatol 2002;14(8):887-90.
4. Braun JS, Geiger R, Wehner H, Schaffer S, Berger M. Hepatitis caused by antidepressive therapy with maprotiline and opipramol. Pharmacopsychiatry 1998; 31(4): 152-5.
5. Lucena MI, Carvajal A, Andrade RJ, Velasco A. Antidepressant-induced hepatotoxicity. Expert opinion on drug safety 2003; 14: 249-62.
6. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al.; Drug Induced Liver Injury Network (DILIN). Causes, Clinical Features, and Outcomes From a Prospective Study of Drug-Induced Liver Injury in the United States. Gastroenterology 2008; 135(6):1924-34.
7. Pollmacher T, Haack M, Schuld A, Kraus T, Hinze-Selch D. Effects of antipsychotic drugs on cytokine networks. J Psychiatric Research 2000;34(6):369-82.
8. Hoek J, Pastorino J. Ethanol, oxidative stress and cytokine-induced liver cell injury. Alcohol 2002; 27(1): 63-8.
9. DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother 2007;41(7):1201-11.
10. Moldawsky RJ. Hepatotoxicity associated with maprotiline therapy: a case report. J Clin Psychiatry 1984; 45(4): 178-9.
11. Murray KF, Hadzic N, Wirth S, Bassett M, Kelly D. Drug-related hepatotoxicity and acute liver failure. J Pediatr Gastroenterol Nutr 2008; 47(5): 395-405.
12. Andrade RJ, Lucena MI, Aguilar J, Lazo MD, Camargo R, Moreno P, et al. Chronic liver injury related to use of bentazepam: an unusual instance of benzodiazepine hepatotoxicity. Dig Dis Sci 2000; 45(7): 1400-4.
13. Kostic V, Djordjevic M, Popovic L, Kostic E, Djordjevic J, Paunovic K. Chronic renal failure associated with hepatitis B and C viruses as a therapy problem. Acta Medica Medianae 2008; 47(3):5-8.
14. Doube A. Hepatitis and non-steroidal anti-inflammatory drugs. Ann Rheum Dis 1990; 49(7): 489-90.
15. Fsadni C, Fsadni P, Piscopo T, Mallia Azzopardi C. Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms syndrome in a 35-year-old man with epilepsy. Clin Neuropharmacol 2008; 31(5): 295-8.

HEPATITIS TOXICA-PRIKAZ BOLESNIKA

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Toksično oštećenje jetre često je predmet diferencijalno dijagnostičkog ispitivanja infektologa hepatologa. Problem se u velikoj meri uvećava unosom propisanih medikamanta kao i njihovim unosom tokom takozvanog samolečenja.

Oštećenje jetre najčešće protiče po tipu holestazne forme bolesti sa ispoljenim kliničkim manifestacijama tipa žutila, pruritusom, promenom boje mokraće i stolice. Klinički nalaz je praćen i karakterističnim laboratorijskim nalazom (bilirubin, alkalna fosfataza, glutamil transpetidaza, holestrol i drugo). U cilju potpune dijagnostike ovakvih bolesnika neophodno je često uraditi biopsiju jetre sa pratećom patohistološkom obradom uzetog materijala. Ispitivana je 42-godišnja bolesnica sa elementima holestaze, kod koje se posle kliničkog i laboratorijskog ispitivanja pribeglo biopsiji jetre, čime je potvrđen toksični karakter oštećenja jetre. Acta Medica Medianae 2009;48(2):49-51.

Ključne reči: *toksični hepatitis, medikamenti*