Euroasia Journal of Mathematics, Engineering, Natural & Medical Sciences
International Indexed & Refereed
ISSN: 2667-6702

EFFICACY OF N-ACETYLCYSTEINE TREATMENT IN METHIMAZOLE-INDUCED MYOPATHY AND TOXIC HEPATITIS (CASE REPORT)

METHİMAZOLE BAĞLI MYOPATİ VE TOKSİK HEPATİTTE N-ASETİLİSİSTEİN TEDAVİSİNİN ETKİNLİĞİ (OLGU RAPORU)

Tahir Buran[1*], Mustafa Sahin[2], Elmas Kasap[1], Semin Ayhan[3], Burcu Almacan[2]

[1]Department of Gastroenterology, Manisa Celal Bayar University

[2]Department of Internal Medicine, Manisa Celal Bayar University

[3]Department of Pathology, Faculty of Medicine, Manisa Celal Bayar University

**Corresponding Author: Tahir Buran*

Geliş Tarihi / Received: 7.08.2020
Kabul Tarihi / Accepted: 20.09.2020

Araştırma Makalesi/Research Article
DOI: 10.38065/euroasiaorg.230

ABSTRACT

Today, antithyroid drugs are widely used in the treatment of hyperthyroidism. Elevated creatine kinase and liver injury (hepatitis) caused by methimazole are some of rare side effects. Elevation of creatine kinase (CK) should be monitored due to the risk of rhabdomyolysis development. Also, drug-induced liver injury can be seen. In this article, we report a patient who was given methimazole 2 months ago for hyperthyroidism, but then began to have complaints about muscle pain, jaundice (icterus) in the eyes along with itching and dark urine, and found out to have elevated creatine kinase as well as liver enzymes induced by liver injury, thus showed rapid recovery upon N-Acetyl Cysteine (NAC) treatment.

Keywords: Hyperthyroidism, Myalgia, Creatine kinase, Liver injury, Elevated liver enzymes, icterus

ÖZET

Günümüzde, antitroid ilaçlar hipertiroidizm tedavisinde yaygın olarak kullanılmaktadır. Metimazolün neden olduğu yüksek kreatin kinaz ve karaciğer hasarı (hepatit) nadir görülen yan etkilerden bazılarıdır. Rabdomiyoliz gelişme riski nedeniyle kreatin kinazın (CK) yüksekliği izlenmelidir. Ayrıca ilaca bağlı karaciğer hasarı görülebilir. Bu yazıda, 2 ay önce hipertiroidi nedeniyle methimazole konulmuş ancak daha sonra gözlerde kaşıntı ve koyu idrar ile birlikte kas ağrısı, sarılık (ikterus) şikayetleri olan ve kreatinin yükseldiği tespit edilen bir hastayı sunuyoruz. kinaz ve ayrıca karaciğer hasarı ile indüklenen karaciğer enzimleri, N-Asetil Sistein (NAC) tedavisi üzerine hızlı iyileşme gösterdi.

Anahtar Kelimeler: Hipertroidizm, metimazol, toksik hepatit, karaciğer hasarı, kretin kinaz

INTRODUCTION

6% of patients treated for hyperthyroidism showed mild side effects such as itching, skin rash and joint pain, etc. These side effects often recover by themselves. In 0,3% of patients, serious side effects such as agranulocytosis, vasculitis, cholestatic hepatitis induced by methimazole are observed (1). Toxic hepatitis in particular is the liver injury caused by the use of drugs, foods and chemicals.

It is difficult for the physicians to diagnose it since several factors might cause liver injury. The liver is the main organ metabolizing a number of chemicals and drugs (2, 3).

Liver injury can manifest itself in different ways, ranging between liver enzymes changes that do not cause any clinical picture, acute hepatitis, prolonged cholestasis, chronic hepatitis, cirrhosis and tumour development and fulminant hepatic failure.

While, in some cases, the symptoms of toxic hepatitis emerge months later, they appear within hours or days of exposure (4).

N-acetylcysteine (NAC) is a glutathione precursor that replenishes the glutathione reservoir in the liver, and it detoxifies the reactive metabolite of acetaminophen. It is a highly effective drug for the prevention of acute liver failure caused by acetaminophen. However, its use is uncertain in alcohol intoxication, hepatic virus infection, or acute liver failure developing due to drug and toxin, which is not induced by acetaminophen (5).

This article serves the purpose of reporting the safety and efficacy of N-Acetyl Cysteine (NAC) treatment administered to the patient who developed myopathy and toxic hepatitis while he was on methimazole due to the treatment of hyperthyroidism.

Case Report

A 69-year-old male patient, who has been on methimazole (20 mg/day) for 2 months for hyperthyroidism, came to our clinic due to yellowing in his eyes and skin, pale stool, dark urine, as well as pain in the arms and legs for a week. He had no fever and abdominal pain, and no itching.

There was no history of alcohol consumption, use of pain relievers or herbal medication, and no history of antibiotic use. He did not have a history of trip to a tropical region, either.

Patient's blood pressure (BP): 120/80 mmHg, Pulse: 76 beats/minute, Temperature: 36.6 °C.

Physical Exam; Scleras and skin are icteric; the liver is tender upon deep palpation on the rib edge; no splenomegaly, ascites, telangiectasia or asterix. The arms and legs were tender during palpation.

Patient's tests were requested; laboratory results are shown in Table-1.

The patient had a moderately high creatine kinase (CK) and lactate dehydrogenase (LDH) enzyme. There was no bilirubin (+++) in urine stick examination and no erythrocyte in microscopic examination.

In addition, Magnetic Resonance Cholangiopancreatography (MRCP) was performed because the patient's laboratory findings were favouring cholestasis.

MRCP: Intra and extra hepatic biliary tracts and choledochus (common bile duct) are in normal diameter, with the lumen open all the way to the papilla vater. The pancreatic duct was not dilated.

Doppler ultrasonography: Liver measuring 142 mm; parenchymal echo is normal. No mass pathology with a sonographically distinctive boundary or echo variation. Portal venous system and main hepatic veins are normal in appearance. The gallbladder is normal; intra and extra hepatic bile ducts were not observed as dilated. The spleen is of normal size, measuring 112 mm along its long axis. Its parenchyma shows normal sonographic structure.

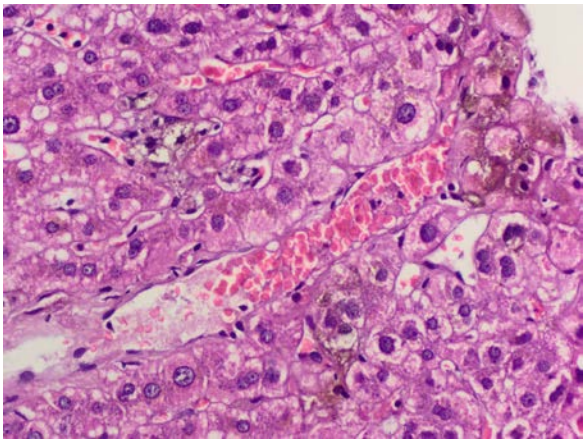
Portal vein diameter is 11 mm; splenic vein diameter is 7 mm; superior mesenteric vein diameter is 8 mm. The direction of flow in these vessels is hepatopedal. No thrombosis was observed in portal venous structures. Intraabdominal free fluid and portosystemic shunt were not observed.

The patient was admitted to our clinic with pre-diagnoses of myopathy, toxic hepatitis, viral hepatitis, autoimmune hepatitis and autoimmune cholangitis, because he did not have a cholestasis that would cause obstruction in the extra hepatic biliary tract.

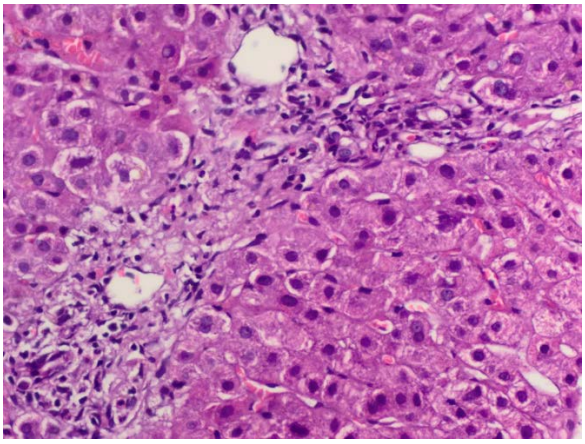
The medical history of the patient who was previously diagnosed with hyperthyroidism, was given methimazole two months ago.

The patient's Alanine amino transferase/Alkaline phosphatase (ALT/ALP) ratio was found out to be 1.12. It was compatible with liver injury of cholestatic type. Besides, Roussel Uclaf Causality Assessment Method (RUCAM) Score was 9. It was compatible with cholestatic liver injury. Liver biopsy was performed on the patient for diagnostic purposes.

Biopsy showed that liver's micro-anatomical structure is maintained; the cell cords are single-line and well organized. Portal areas are enlarged due to oedema and mixed inflammatory cell infiltration. Remarkably, 2-3 eosinophils are observed in almost each portal area. A large focus consisting of hemosiderin-laden macrophages was observed in a portal area. In the parenchyma, bile stasis, which creates plugs especially in areas that fit around the central vein, is observed. HBsAg immune stain was negative. (Picture-1,2)



Picture 1: Bile plugs and bile stasis (HE, x40)



Picture 2: Remarkable eosinophils in the area of edema and mild inflammatory infiltration monitoring portal area (HE, x40)

Therefore, viral etiology was not considered. The findings identified were compatible with toxic hepatitis.2

After ruling out the causes that could lead to the patient's hepatitis picture, liver injury was thought to have been induced by methimazole.

Bolus intravenous (IV) 150 mg/kg of N-Acetyl cysteine infusion was administered on 09.03.2020 while the patient with Model for End-Stage Liver Disease (MELD) score above 20 was prepared for liver transplantation for. The infusion was followed by maintenance treatment, which was continued for 7 days at an infusion dose of 12 mg/kg/day. Intravenous bolus infusion therapy produced over 50% decrease in transaminases and bilirubin levels in 2 days' time (Table 2-3). Also, the MELD score began to drop, too. Table-4).

The patient was discharged 9 days after his hospitalization, as he recovered significantly based on clinical and laboratory findings.

Table 1. Laboratory results of the patient

	Normal range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 40
Haemoglobin	13.6-17.2gr/dl	12.2	11.9	12	12.4	12.2	11.9	12	11.6	12.1	12,9
Leucocyte	4.5-10.3 µL	6.08	7.09	8.77	7.64	8.03	8.55	8.3	7.79	10.03	6,52
Neutrophil	2.1-6.1	4.55	5.6	6.71	5.28	5.39	5.78	5.38	5.32	6.75	3,18
Lymphocyte	1.3-3.5	0.88	1.11	1.2	1.53	1.69	1.79	1.84	1.4	2.09	2,4
Monocyte	0.3-0.8	0.37	0.22	0.47	0.42	0.49	0.42	0.52	0.46	0.65	0,44
Eosinophil	0-0.5	0.25	0.14	0.36	0.38	0.41	0.51	0.51	0.57	0.48	0,42
Thrombocyte	156-373.000µL	149	171	179	221	239	269	269	278	332	258
AST	0-50 Ü/L	311	283	233	234	130	74	52	44	37	22
ALT	0-50 Ü/L	424	437	416	382	307	227	169	149	95	19
GGT	0-55 Ü/L	1584	1585	1466	1397	1393	1302	1078	970	735	120
ALP	30-120 Ü/L	499	463	540	690	656	556	488	370	401	113
Total Bilirubin	0.3-1.2 Mg/dl	13.82	17.32	17.33	8.91	6.22	4.8	4.16	4.12	3.3	1,3
Direk Bilirubin	0-0.2 mg/dl	8.13	8.22	7.72	4.55	2.8	2.01	1.82	1.55	1.39	0,1
Creatinine	0.51-0.95 mg/dl	0.71	0.9	1.06	0.73	0.76	0.72	0.82	0.9	0.86	1,1
Urea	47 mg/dl	47									

PTZ	9.2-12.8 ´´	13	12.9	14.4	14.2	13.4	12.8	12.4	12.9	12.7	12.0
INR	0.8-1.2	1.1	1.09	1.22	1.2	1.13	1.08	1.05	1.09	1.1	1.0
CRP	0-0.5 mg/dl	1.4	1.13	0.86	1		1	1	1.44	1.1	0.1
procalcitonin	0.2 ng/ml	0.2	0.2	0.2			0.2	0.2	0.1	0.1	
IgG	700-1600		711								
IgM	40-230		249								
IgA	70-400		266								
MELD Score	<10	17	20	23	20	20	16	12	14	12	8
HBs Ag	<0.99		Negative								
Anti HBs	<8		Positive								
Anti HCV	0-0.8		Negative								
Anti HAV IGM			Negative								
Anti HBcIgM			Negative								
Erbstain-Bar			Negative								
Sitomegalo Virus			Negative								
Herpes simplex			Negative								
Anti HIV			Negative								
ANA			Negative								
AMA			Negative								
ASMA			Negative								
AMA-M2			Negative								
Anti-LKM			Negative								
Free T4	0.61-1.3 ng/dl			0,68						0.72	
TSH	0.38-5.33u/L			0,07						0.08	
Na	136-146 mEq/L	134	137	134	134	131	137	138	136	137	143
K	3.5-5.1 mEq/L	4.8	3.7	4.5	3.9	3.9	4.2	5.1	4.1	5.1	82
LDH	0-248 U/L	434	432	387	323	247	227	212	218	224	207
Creatine Kinase (CK)	0-171 U/L	1069		455		189	178			168	91
Amylase	28-100	38	33	27	39	39	41	57	56	73	66
Lipase	0-6 Ü/L	36	25	86	30	22	21	29	31	40	22
Albumin	3.5-5.2 g/dl	3.7	3.4	3.2	3.5	3.5	3.5	3.6	3.4	3.8	4,6
Glucose	74-106 mg/dl	97	162	112	108	114	107	106	104	137	82

Table 2. Progress of liver enzyme levels of the patient

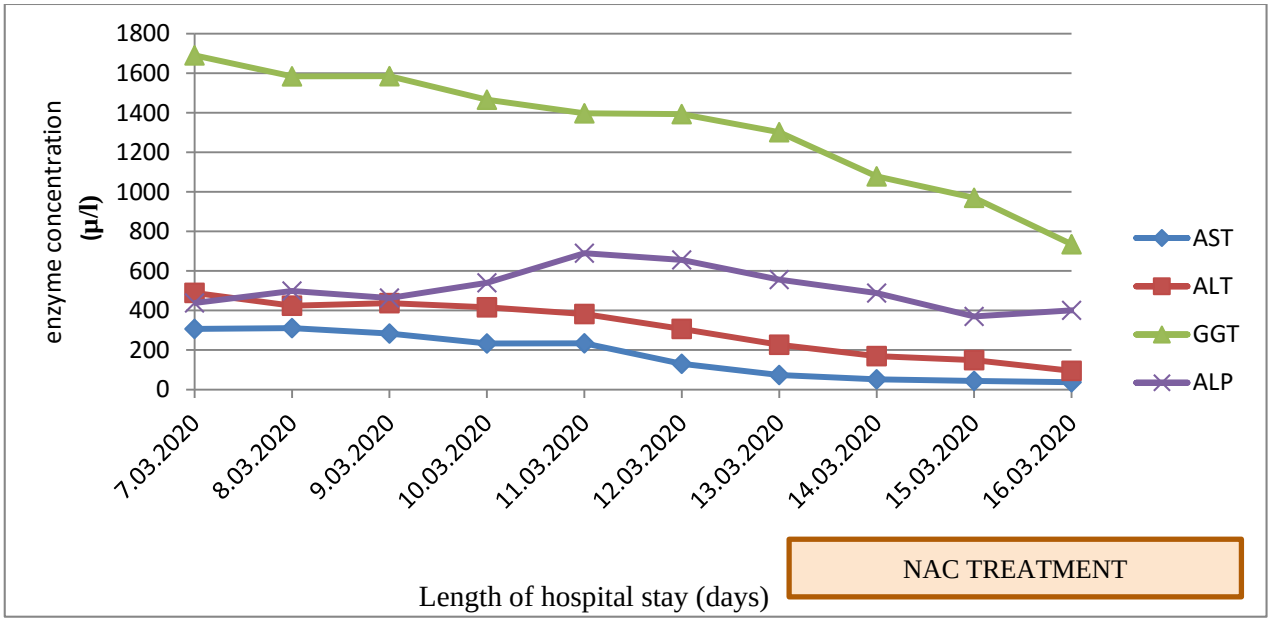


Table 3. Progress of total bilirubin level of the patient.

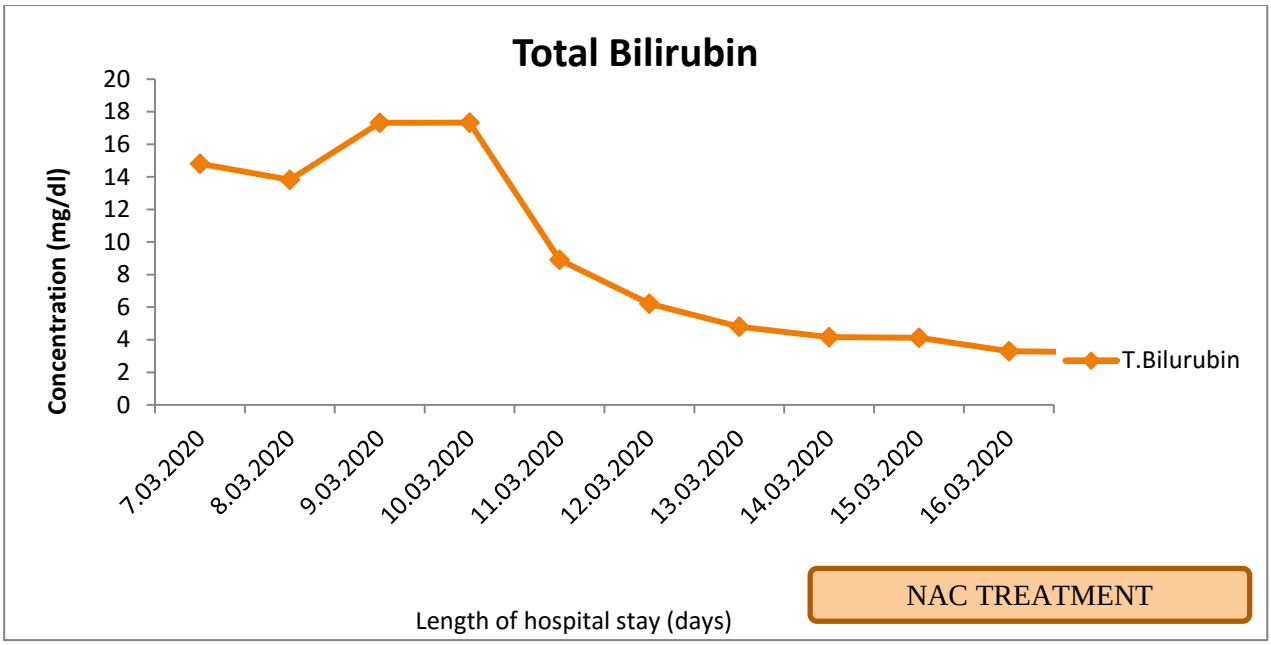
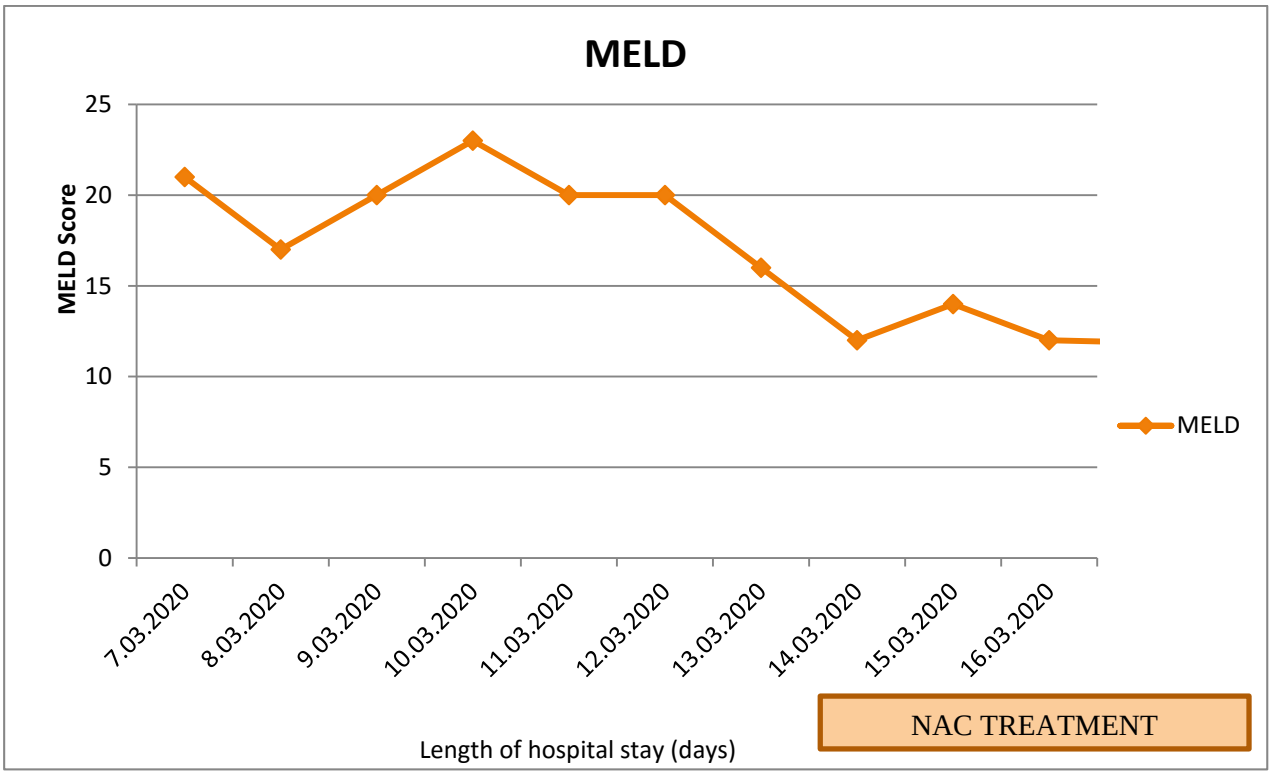


Table 4. Change in MELD Score of the patient



DISCUSSION

Drug-induced myopathy is one of the common causes of muscle diseases and occurs directly as a result of myotoxicity, inflammatory myopathy, indirect muscle damage or combined mechanisms (6, 7). Suzuki et al. found out that the complaints decreased after the dose of methimazole was reduced and levothyroxine was added to the treatment in four adult Graves patients with elevated creatine kinase induced by methimazole treatment (8). Ito et al. reported that a patient suffered myalgia and

elevated creatine kinase due to methimazole, and the complaints subsided as soon as medication was discontinued (9).

Although the cause of elevated creatine kinase that emerges following the treatment with methimazole cannot be fully explained, it is suggested that it can be caused by relative hypothyroidism that occurs rapidly in the tissues following the hyperthyroidism treatment (10, 11). In our case, when the patient came to our clinic, free T4 level was at the lower limit of the range while TSH was below the normal limits. The patient had no more pains once the methimazole treatment was stopped. CK and LDH levels improved to normal. Benign acute drug-induced myositis was considered because the patient was not considered to have serious muscle damage and had moderately elevated CK and LDH levels. Electromyography (EMG) was not performed since our patient was not considered for rhabdomyolysis.

As a conclusion, serum muscle enzymes (e.g. CK and LDH) should be checked, the use of medication can be discontinued, where necessary, and proper hydration and NAC treatment can be recommended in the patients who take methimazole and apply for complaints of myalgia.

The picture of drug-induced toxic hepatitis is one of the most challenging clinical conditions in hepatology. This is due to the herbs and dietary supplements posing hepatotoxic potential, in addition to the high number of drugs used in clinical practice, low incidence rate compared to other acute or chronic liver disease, and absence of specific markers that can distinguish drug-related toxic hepatitis from other liver disorders. All these factors make it difficult to diagnose drug-induced toxic hepatitis. Additionally, early diagnosis is very crucial since acute liver failure developing after drug-induced toxic hepatitis involves a poor prognosis (12).

The exact mechanism of methimazole-induced hepatotoxicity is unknown. Hypersensitivity and drug reactions are the common hypotheses. Cell-mediated immunity may also play a role in causing cholestatic hepatitis in patients treated with methimazole (13). When lymphocytes are triggered by a particular drug, the resultant lymphokines may lead to cholestasis by causing a decrease in bile flow (14). The most common type of hepatotoxicity seen in the use of Methimazole is the cholestatic liver injury (15, 16, 17). In our case, R: ALT/ALP is 1.12 ($R \leq 2$) and compatible with cholestatic liver injury, in support of the literature (18, 19).

Liver biopsy may show the traces of portal enlarged with inflammatory cells, and also biliary plugs may be seen. Widespread swelling of hepatocytes is another feature that can be seen (20, 21, 22). The onset of symptoms can vary between a few days up to 150 days (23). In our case, the liver injury caused by methimazole developed in a period less than 2 months.

In the case of drug-induced toxic hepatitis, the first line of treatment is the discontinuation of the drug leading to the picture.

Although N-Acetylcysteine therapy is primarily recommended in acetaminophen intoxication in the literature, it has been observed in recent studies that it improves the rate of survival and recovery in the case of drug-induced acute liver failure (24). N-acetyl cysteine (NAC) is a drug widely used for mucolytic purposes, especially in the treatment of lung diseases as it facilitates the excretion of mucus (24). In acetaminophen poisoning due to overdose, it plays an important role as antidote as part of the treatment (25, 26). However, it is also recommended for the treatment of acute liver failures developing due to non-acetaminophen related causes. The dose recommended for NAC treatment can vary between 100-200 mg/kg/day depending on the age of the patient (5, 27, 29).

Our patient was initially treated with 150 mg/kg of loading dose as IV bolus, which was followed by the treatment with IV infusion of N-Acetyl Cysteine 12 mg/kg for 7 days. Liver enzymes (Table-1, 2) and bilirubins (Table-1, 3) improved dramatically. The MELD Score has declined significantly. The graph in Table-4 shows the change in MELD Score. Some rare side effects such as rash and mild itching, etc., which do not require any treatment, can be seen at a rate 14.3% in the treatment with NAC (25). Our patient showed no side effects caused by the treatment. On the 40th day of treatment, the patient's liver enzymes and MELD score returned to normal.

CONCLUSION

Drug-induced toxic hepatitis is diagnosed with proper clinical and laboratory tests once the causes leading to hepatitis are ruled out.

As soon as the diagnosis is established, the causing agent should be discontinued and preparation for transplantation should be done. Preparation for transplantation is still required even if the particular case suggests a low possibility of transplantation, as in the case of our patient. Therefore, we advocate the idea that N-acetyl cysteine (NAC) treatment plays an important role both prior to transplantation and in the process of recovery, similarly in our patient in line with the recent studies in the literature. We believe that N-acetylcysteine treatment should be considered primarily in the case of toxic hepatitis, considering its poor side effects.

REFERENCES

1. Larrooy Jameson J L, De Groot L J (Editors). Endocrinology Adult and Pediatric 7.th edition. Philadelphia; Elsevier-Saunders: 2015. p. 1456-7.

2. Arıcı S. Toksik Hepatit. Pamukkale Tıp Dergisi 2008;1:113-9.

3. Karsen H, Çalışır C, Duygu F ve ark. Zayıflama çayı kullanımına bağlı gelişen akut hepatit: Bir Olgu Sunumu. Van Tıp Dergisi 2011;18:110-2.

4. Bonkovsky HL, Jones DP, LaBrecque DR, Shedlofsky S. Drug-Induced Lıver Injury. In: Boyer TD, Wright TL, Manns MP, Editors. Zakim and Boyer's Hepatology, A Textbook Of Liver Disease. Volume I, 5th,Saunders. Elsevier 2006;503-50.

5. Hu J, Zhang Q, Ren X, Sun Z, Quan Q. Efficacy and safety of acetylcysteine in "nonacetaminophen" acute liver failure: A meta-analysis of prospective clinical trials. Clin Res Hepatol Gastroenterol 2015; 39(5):594-9.

6. Lane RJ, Mastaglia FL. Drug-induced myopatihesin man. Lancet. 1978;2:562-6.

7. Sieb JP, Gillessen T. Iatrojenic and toxic myopathies. Muscle Nerve. 2003; 27:142.

8. Suzuki S, et al. Elevation of serum creatine kinase during treatment with anti-thyroid drugs in patients with hyperthyroidism due to Graves' disease. A novel side effect of anti-thyroid drugs. Arch Intern Med. 1997;157:693-6.

9. Ito T, Katahira M, Hanakita M, Suzuki. A case of elevation of serum creatine kinase with anti-thyroid medications for Graves' disease. J Endocrinol Metab. 2012;2:244-7.

10. Mizuno H, et al. Elevation of serum creatine kinase in response to medical treatment of Graves' disease in children. Acta Paediatr. 2006;243-5.

11. Kim H, et al. Elevation of serum creatinine kinase during methimazole treatment of Graves' disease in a 13-year-old girl and a literature review of similar cases. Ann Pediatr Endocrinol Metab. 2015;20:106-9.

12. Hillman L, Gottfried M, Whitsett M, et al. Clinical features and outcomes of complementary and alternative medicine induced acute liver failure and injury. Am J Gastroenterol. 2016;111:958-965.

13.E Arab D, Malatjalian DA, Rittmaster RS.Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. J Clin Endocrinol Metab 1995;80(4):1083-5.

14.F Blom H, Stolk J, Schreuder HB, et al. A case of carbimazole-induced intrahepatic cholestasis. An immunemediated reaction? Arch Intern Med 1985;145(8):1513-15.

15. Rivkees S, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab 2010;95(7):3260-7.

16. Gallelli L, Staltari O, Palleria C, et al. Hepatotoxicity induced by methimazole in a previously healthy patient.Curr Drug Saf 2009;4(3):204-6.

17. Woeber K. Methimazole-induced hepatotoxicity. Endocr Pract 2002;8(3):222-4.

18. Noureddin N., Kaplowitz N. Overview of mechanisms of drug-induced liver injury (DILI) and key challenges in DILI research. In: Chen M., Will Y., editors. DRUG-INDUCED LIVER TOXICITY. METHODS IN PHARMACOLOGY AND TOXICOLOGY. New York, NY, USA: Humana Press; 2018. pp.3–18.

19. Holt M. P. Ju C. Mechanisms of drug-induced liver injury. AAPS JOURNAL. 2006;8(1):48-54.

20.Shen C, Zhao CY, Liu F, et al. Acute-on-chronic liver failure due to thiamazole in a patient with hyperthyroidism and trilogy of Fallot: case report. BMC Gastroenterol 2010;10:93.

21.Majeed M, Babu A. Cholestasis secondary to hyperthyroidism made worse by methimazole. Am J Med Sci 2006;332(1):51-3.

22. Hung Y, Yu WK, Chow E. Delayed cholestatic hepatitis due to methimazole.Hong Kong Med J 1999;5(2):200-1.

23. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856–864.

24. Johnson K, McEvoy CE, Naqvi S, et al. Highdose oral N-acetylcysteine fails to improve respiratory health status in patients with chronic obstructive pulmonary disease and chronic bronchitis: a randomized, placebo-controlled trial. Int J Chron Obstruct Pulmon Dis 2016;11:799-807.

25. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous Nacetylcysteine treatment protocol. Ann Emerg Med 1991;20(10):1058–63.

26. Bucaretchi F, Fernandes CB, Branco MM, et al. Acute liver failure in a term neonate after repeated paracetamol administration. Rev Paul Pediatr 2014;32(1):144-8.

27. Dart RC, Erdman AR, Olson KR, et al. Acetaminophen poisoning: An evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44(1):1-18.

28. Mumtaz K, Azam Z, Hamid S, et al. Role of Nacetylcysteine in adults with non-acetaminopheninduced acute liver failure in a center without the facility of liver transplantation. Hepatol Int 2009; 3(4): 563-70.

29. Saleem AF, Abbas Q, Haque AU. Use of Nacetylcysteine in children with fulminant hepatic failure caused by acute viral hepatitis. J Coll Physicians Surg Pak. 2015; 25(5):354-8.