CASE REPORT

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Efficacy of N-acetylcysteine Treatment in Methimazole-induced Myopathy and Toxic Hepatitis

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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 received methimazole 2 months ago for hyperthyroidism, but then began to have complaints like muscle pain, jaundice (icterus) in the eyes along with itching and dark urine, and found out to have elevated CK as well as liver enzymes induced by liver injury, thus showed rapid recovery upon N-acetylcysteine treatment.

Keywords: Hyperthyroidism; myalgia; creatine kinase; liver injury; icterus

Of patients treated for hyperthyroidism, 6% showed mild side effects such as itching, skin rash and joint pain, etc. These side effects often recover spontaneously. In 0.3% of the patients, serious side effects such as agranulocytosis, vasculitis, cholestatic hepatitis induced by methimazole are observed.[1,2] 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 enzyme 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 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-acetylcysteine (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, was admitted to our clinic due to yellowing in his eyes and skin, pale stool, dark urine, as well as

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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. On physical examination; Sclera and skin were icteric, liver was tender upon deep palpation on the rib edge; no splenomegaly, ascites, telangiectasia or asterix was observed. The arms and legs were tender during palpation. Laboratory test results are shown in Table 1. The patient had a moderately high creatine kinase (CK) and lactate dehydrogenase (LDH) enzyme. There was 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 and doppler ultrasonography were normal. 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 revealed methimazole treatment two months ago. The patient's alanine amino transferase/alkaline phosphatase (ALT/ALP) ratio was found 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 for diagnostic purposes. Biopsy showed that liver's micro-anatomical structure was preserved, the cell cords were single-line and well organized. Portal areas were enlarged due to oedema and mixed inflammatory cell infiltration. Remarkably, 2-3 eosinophils were 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 was observed. HBsAg immune stain was negative (Figure 1, Figure 2).

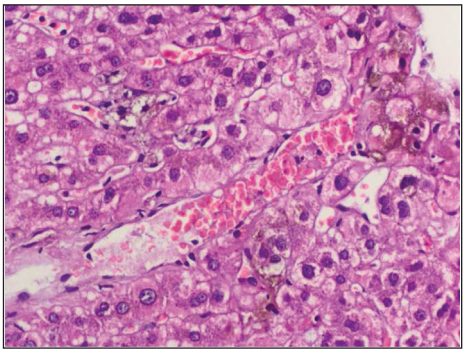


FIGURE 1: Bile plugs and bile stasis (HE, x40).

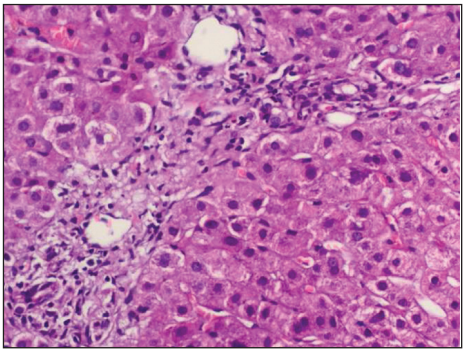


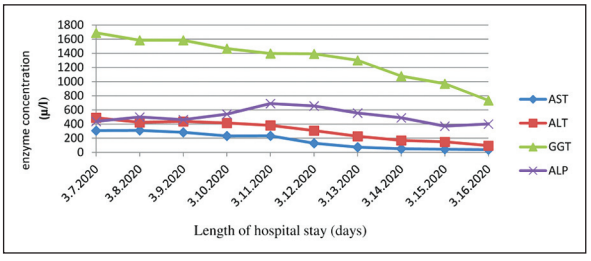
FIGURE 2: Remarkable eosinophils in the area of edema and mild inflammatory infiltration monitoring portal area (HE, x40).

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

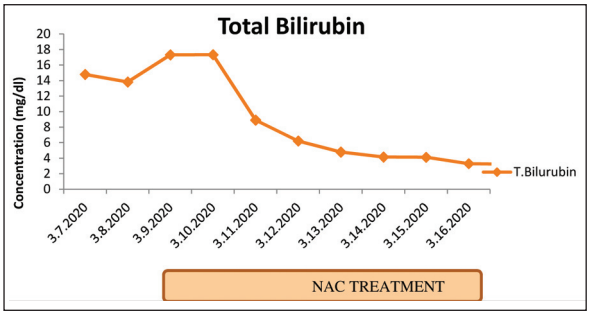
Bolus intravenous (IV) 150 mg/kg of NAC infusion was administered on 09.03.2020 while the patient with Model for End-Stage Liver Disease (MELD) score above 20 was prepared for liver transplantation. The infusion was followed by maintenance treatment, which was continued for 7 days at an infusion dose of 12 mg/kg/day. Intravenous bolus infusion therapy produced over 50% decrease in transaminases and bilirubin levels in 2 days time (Graphic 1, Graphic 2). Also, the MELD score began to decrease (Graphic 3). The patient was discharged 9 days after his hospitalization, as he recovered significantly based on clinical and laboratory findings.

DISCUSSION

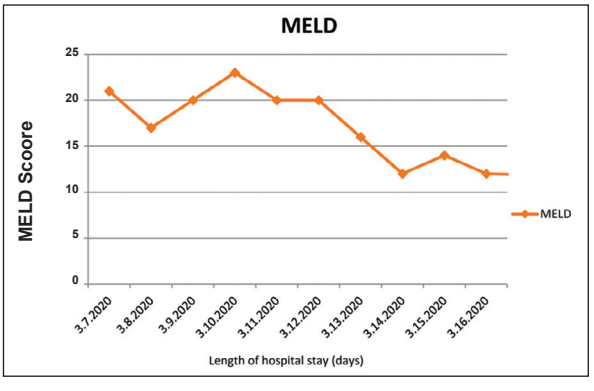
Drug-induced myopathy is one of the common causes of muscle diseases and occurs directly as a result of myotoxicity, inflammatory myopathy, indirect muscle



GRAPHIC 1: Progress of liver enzyme levels.



GRAPHIC 2: Progress of total bilirubin level.



GRAPHIC 3: Change in Model for End-Stage Liver Disease (MELD) score.

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] In our patient 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. CK and LDH levels normalized after stopping methimazole.

The picture of drug-induced toxic hepatitis is one of the most conflicting clinical conditions in hepatology. Early diagnosis is very crucial since acute liver failure developing after drug-induced toxic hepatitis involves a poor prognosis.[10] 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.[11] When lymphocytes are triggered by a particular drug, the resultant lymphokines may lead to cholestasis by causing a decrease in bile flow.[12] The most common type of hepatotoxicity seen in the use of methimazole is the cholestatic liver injury.[13-15] In our case, R: ALT/ALP was 1.12 (R≤2) and compatible with cholestatic liver injury. 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.[16-18] The onset of symptoms can vary between a few days up to 150 days.[19] In our case, the liver injury caused by methimazole developed in a period less than 2 months. NAC 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.

NAC is a drug widely used for mucolytic purposes, especially in the treatment of lung diseases as it facilitates the excretion of mucus.[20] In acetaminophen poisoning due to overdose, it plays an important role as antidote as part of the treatment.[21,22] 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.[5,23,24] 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 NAC 12 mg/kg for 7 days. Liver enzymes (Table 1 and Graphic 1) and bilirubins (Table 1 and Graphic 2) improved dramatically. The MELD score has declined significantly

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
Leukocyte	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
Platelet	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								
Ebstein Barr Virus			Negative								
Cytomegalo Virus			Negative								
Herpes Simplex Virus			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

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase, PTZ: Protrombin Time, INR: International normalized ratio, CRP: C-reactive protein, Ig G: İmmünoglobulin Gİ Ig A: İmmünoglobulin A, IG M: İmmünoglobulin M, MELD Score: Model for End-Stage Liver Disease Score, Hbs Ag: Hepatitis B surface Antigen, Anti-Hbs: Hepatitis B surface Antibody, Anti-HCV: Hepatitis C Antibody, Anti HAV Ig M: Hepatitis A Antibody İmmünoglobulin M, Anti Hbc IgM: Hepatitis B core antibody immünoglobulin M, Anti HIV: Human Immunodeficiency Virus Antibody, ANA: Antinuclear Antibodies, AMA: Antimitochondrial antibody, ASMA: Anti-smooth muscle antibody, AMA-M2: Anti-mitochondrial M2 antibody, Anti-LKM: Liver-Kidney Microsome Antibodies, TSH: Thyroid Stimulating Hormone, Na: Sodium, K: Potassium, LDH: Lactate Dehydrogenase.

(Graphic 3). Some rare side effects such as rash and mild itching, etc., which do not require any treatment, can be seen in the treatment with NAC.[21] 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. 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.

Informed Consent

Written informed consent was obtained.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tahir Buran, Elmas Kasap, Mustafa Sahin;* ***Design:*** *Tahir Buran;* ***Control/Supervision:*** *Tahir Buran, Elmas Kasap;* ***Data Collection and/or Processing:*** *Mustafa Sahin,Burcu Almacan İnce;* ***Analysis and/or Interpretation:*** *Tahir Buran;* ***Literature Review:*** *Tahir Buran, Mustafa Sahin;* ***Writing the Article:*** *Tahir Buran, Mustafa Sahin, Elmas Kasap;* ***Critical Review:*** *Elmas Kasap, Tahir Buran;* ***References and Fundings:*** *Tahir Buran;* ***Materials:*** *Tahir Buran.*

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