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Journal of Infectious Diseases & Preventive Medicine

Case Report

Acute Liver Injury and Pancytopenia Subsequent to Cephalexin and Dexketoprofen Use: A Case Report

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Abstract

Elevated serum transaminases and pancytopenia related to medication are rarely seen adverse effects that could lead to serious consequences. A 37-year-old patient, who was admitted to an infection clinic with signs including fever, elevated liver enzymes and pancytopenia that developed subsequent to cephalexin and dexketoprofen trometamol use due to acute upper respiratory tract infection was presented in this report. Dexketoprofen and cephalexin, which are commonly prescribed to treat acute respiratory tract infections together at ambulatory or emergency clinics, may cause a life-threatening side effect, such as pancytopenia and acute liver injury.

Keywords: Elevated serum; Pancytopenia; Liver enzymes; Acute liver injury

Abbreviations:

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALF: Acute Liver Failure; DILI: Drug Induced Liver Injury; DILIN: Drug Induced Liver Injury Network

Introduction

Fever is defined as an elevation in the body temperature above the daily range related to most infections and also non-infectious diseases, such as autoimmune and auto-inflammatory diseases, trauma, malignancy and autoimmune diseases. Drug induced fever, brain injury and endocrine diseases are other rare causes of fever [1].

Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) release from injured hepatocytes leading to increased serum levels. In the differential diagnosis of elevated serum aminotransferases, viral hepatitis, hepatotoxicity related to drugs or toxins, alcoholic liver disease, ischemic hepatitis, and a malignant infiltration are the main causes. Drug-induced liver injury was reported to be responsible for about 50% of Acute Liver Failure (ALF) cases in the United States. Many weight loss medications, over-the-counter medications, dietary supplements, and prescription medications can cause to acute liver injury [2]. Drug-related liver injury may be dose-dependent and presumable (acetaminophen toxicity) or idiosyncratic, and unpredictable (carbamazepine, valproate). Idiosyncratic drug-related hepatotoxicity can develop within six months of drug therapy. A detailed medication history is essential and should comprise the dosage, therapy start, duration of treatment, and last dose. A history concerning recent mushroom ingestion and use of herbal products should also be elicited. The mortality rate of acute liver injury today ranges from 30% to 40% [2]. The mortality risk of a patient with Drug Induced Liver Injury (DILI) can be assessed based on an objective severity grading made by the Drug-Induced Liver Injury Network (DILIN). This grading is based on ALT, AST, bilirubin levels and INR values of the patient [3].

Pancytopenia is defined as a decrease in all three cell lines below the normal reference range. Factors leading to pancytopenia vary depends on the patient's age, gender, geographical location. The main reasons leading to pancytopenia are Vitamin B12 deficiency, chronic liver disease, malignancy, myelodysplastic syndrome, aplastic anemia, rheumatic diseases, and endocrine causes. The diagnosis process involves different laboratory test, radiological examinations and invasive procedures, such as a bone marrow biopsy, if it is needed [4].

In this case report, we presented a patient who was admitted with signs including fever, elevated liver enzymes and pancytopenia that developed subsequent to cephalexin and dexketoprofen trometamol use.

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Received : December 27, 2018; **Accepted :** January 19, 2019; **Published** : January 25, 2019

Citation: Gedik H, Sönmezışık M (2019) Acute Liver Injury and Pancytopenia Subsequent to Cephalexin and Dexketoprofen Use: A Case Report. J Infect Dis Preve Med 7:186. doi: 10.4172/2329-8731.7.186

Case Report

A 37-year-old man was admitted to the infectious diseases clinic with the complaints of fever lasting for 20 days, fatigue, diarrhea, and vomiting in the last three days. He had applied to an emergency service with the complaint of fever lasting 10 days before admission to our clinic and then cephalexin and dexketoprofen trometamol were prescribed. His complaints had deteriorated under those medications and he had applied to our clinic discontinuing those drugs. He had reported that laboratory tests were normal in the first admission to emergency service and acute upper respiratory tract infection was diagnosed. In medical history, he had an unprotected sexual discourse and urethral discharge two months ago. He was smoking one pack/day, but had no a history of alcohol and substance use, a chemical substance exposure, a blood transfusion, a surgery, a drug hypersensitivity, and any other medications. Physical examination and vital signs were normal except for a fever of 39°C at the admission. Laboratory tests revealed white blood cell count (WBC) of $1.11X10^3/\mu L$, hemoglobin (Hgb) 11.4 g/dL, platelet (PLT) 69 X $10^3/\mu L$, alanine transaminase (ALT) of 1084 IU/L, aspartate transaminase (AST) of 2809 IU/L, gamma-glutamyl transpeptidase (GGT) of 153 IU/L, lactate dehydrogenase (LDH) of 967 IU/L, creatine kinase (CK) of 912 IU/L, whereas the other laboratory tests were within the normal range (Table 1).

In the complete urinalysis, hematuria, ketonuria and albuminuria were detected. Abdominal ultrasonography revealed normal findings. An empirical cefotaxime therapy (3X2 gr) intravenously (IV) was initiated taking into consideration its renal elimination. Fever persisted to be 39°C on the second day of hospitalization and the antimicrobial therapy was changed to piperacillin/tazobactam 3 X 4.5 gr IV due to possible resistant bacteria secondary to leukopenia. Gastroenterology physician revealed in the consultation that elevated liver enzymes were not related to a primary liver disease, but should be evaluated in the context of medications and infectious diseases. Abdominal computed tomography (CT) scan with contrast agent recommended by gastroenterology physician revealed multiple lymph nodes less than 1 cm in the mesenteric adipose tissue located in the right lower quadrant and a minimal free fluid collection in the anterior region of the rectum. Thoracic CT scan revealed multiple lymph nodes not exceeding 1 cm in upper and lower paratracheal neighborhoods, the pleural effusion with a vertical size of 29 mm in the left hemithorax and 8mm in the right hemithorax, an atelectasis in the adjacent areas of effusion, an increased peribronchial density in both hilar and perihilar neighborhoods, frosted glass densities and thickening of interlobular septal structures at both upper and lower lobe levels of lungs, and bilateral perihilar sequels. Fever defervesced under the antibiotic treatment and elevated liver enzymes commenced to decrease (Table 1). In the serum protein electrophoresis, decreased albumin and total protein values and increased levels of Alpha-1 and Beta-1 globulins were detected. Transthoracic echocardiography revealed a tricuspid regurgitation, but no vegetation or thrombus. The patient was consulted with the hematology department due to pancytopenia with the peripheral blood smear. On the third day of hospitalization DIC developed and then five units of fresh frozen plasma and eight units of cryoprecipitate were supplemented. Cervical (neck) CT scan was performed to screen a lymphadenopathy. It revealed multiple lymph nodes with a size of 13 X 7 mm in the proximity of the right parotid gland and 14 X 4.5 mm in the proximity of the left parotid gland. On the fourth day of hospitalization, a bone marrow biopsy was performed by hematology physician. Samples were submitted to the pathology department.

After one hour of the bone marrow biopsy, he was desaturated (SpO2:85%) and then mask oxygen was administered. A cardiac arrest developed within a short time and he was resuscitated for 25 min until ECG indicated the sinus rhythm. Piperacillin/tazobactam was changed to imipenem/cilastatine (4 X 500 mg IV) taking into consideration septic shock and then the patient was referred to an intensive care unit. He died within 24 hours of admission to the intensive care unit.

The flowcytometric, immunophotyping and cytological examinations of bone marrow aspirate were reported after one month of the patient's death. It was overly hypocellular, whereas the T/B lymphocyte proportion was reversed, and T lymphocytes were highly depressed (0.6% of the whole cellularity). B lymphoid cells were in the mature profile. There was not an evidence of blast increment.

Table 1: The laboratory findings of the patient.

	19/05	20/05	21/05	22/05	23/05
Alanine Aminotransferase (ALT, N: 0-50 IU/L)	1084	715	513.4	434.1	396
Aspartate Aminotransferase (AST, N: 0-50 IU/L)	2809	1866	1418.7	1337.3	1268
Gamma-glutamyl Transpeptidase (GGT, N: 5-36 IU/L)	153	131	134	190	
Alkaline Phosphatase (ALP, N: 30-120 IU/L)		111		196	
Lactate Dehydrogenase (LDH, N: 135-248 IU/L)	967	10262	9272	9039	8120
Amylase (N:<100 U/L)	80	76	90	118	98
Lipase (N:0-67 U/L)	82	112.5	115	81	91
C- Reactive Protein (N: <0.5 mg/dl)	4.1	4.23	5.35	4.91	4.13
Creatinin Kinase (N: 0-170 U/L)	912	675	641		
Creatinine (N:0.5-1,2 mg/dL)	1.05	0.8	0.87	1.01	1.4

Urea (N: 17-43 mg/dL)	31	22	21	24,1	40
Glucose (N: 74-106 mg/dL)	98	86	83.6	95.2	231
Troponin I (N: 0-17,5)	58	83		80	
Fibrinogen (N: 200-400)		70.9		86.1	
White Blood Cells (WBC, $10^3/mm^3$)	1.11	1.31	1.18	0.77	1.41
Red Blood Cells (RBC, 10^6/ mm3)	4.09	3.94	3.41	2.97	3.33
Platelet (PLT, 103/mm3)	69	75	75	84	132
Hematocrit (Htc, %)	32.9	31.8	25.7	23.1	27.1
Hemoglobin (Hgb, g/dL)	11.4	11	9.4	8.5	9.4
Prothrombin Time (PT, N: 10.7-14.7 sn)	13.4	13.8	15.9	15.1	14
International Normalized Ratio (INR)	1.23	1.27	1.34	1.54	1.35

Discussion

Fever, elevated liver enzymes and pancytopenia were main findings of our case whose fatigue, diarrhea, and vomiting caused the admission to the infectious diseases ward. Cefotaxime, which is eliminated by urine, has been initiated intravenously, as findings suggested a bacterial infection. Test results were negative for common infectious diseases, including EBV, Parvovirus, HIV, Toxoplasma, Rubella, CMV, Leptospirosis, and Hepatitis A-B-C. The bone marrow biopsy was performed by a hematology physician to differentiate the hematological diseases in context with lymphadenopathies revealed in the thorax and abdomen CT scans and pancytopenia. However, there was no finding related to a hematological malignancy in the bone marrow biopsy. Drug related pancytopenia was considered, but it could not be possible to find out which drug caused those signs or whether both drugs caused those signs together. Since side effects, including anemia, decrease in lymphocyte and neutrophil counts in less than a month were reported in a study including 48 people who received cephalexin and dexketoprofen together. Rhabdomyolysis (increased CK level) was reported to be more often in male cases than female cases [5]. Dexketoprofen and cephalexin treatment were likely to cause these signs. Acute liver injury is a rare but life threatening side effect of many drugs, including dexketoprofen and cephalexin that is frequently prescribed to treat infections as in our case. Bonaventure et al. reported a 23-year-old woman who developed elevated liver enzymes (ALT up to 30, AST up to 14 times) after four days of ketoprofen use for the low back pain in a case report [6]. Our case had a mild liver injury, according to DILIN. Mortality risk was not high, when other signs of the case were taken into consideration. Dexketoprofen is a very commonly used over-the-counter non-steroidal anti-inflammatory drug (NSAID) that relieves pain mainly by inhibiting cyclooxygenase 1-2. It is metabolized mainly in the liver, but the mechanism of the liver toxicity is not clear and thought to be an idiosyncratic reaction during its metabolism. The morbidity of ketoprofen hepatotoxicity ranges between mild elevations in serum aminotransferases and symptomatic hepatitis, jaundice. A fulminant hepatitis case was reported due to ketoprofen toxicity, but the case died of pancreatitis and renal insufficiency. Naproxen and ibuprofen should be avoided in patients with ketoprofen induced liver toxicity. It was reported that elevated serum aminotransferases occurred in 1% to 2% of the patients, whereas more than three folds increments developed in less than 1% of the patients under dexketoprofen therapy [7]. Donati et al. reported that 97 of the 179 cases with a Drug Induced Liver Injury (DILI) were exposed to NSAIDs [8]. Zabala S et al. reported a 35 year-old woman who developed fever 5 days after taking dexketoprofen (bilirubin 0.5 mg/dL, ALT 216 U/L, with low platelet (94,000/μL) and white cell counts (1,600/μL) [9]. However, anemia was not reported in this case.

Cephalexin, a first generation oral cephalosporin, is widely being used, especially in the treatment of soft tissue and acute upper respiratory tract infections. Side effects including abdominal pain and diarrhea are common as our case complained. Although serum transaminases might increase up to three-fold elevation under cephalexin use, DILI is rarely seen. Skoog et al. reported a 51 year-old case who developed a fever, jaundice and skin eruption after using cephalexin for ten days, whose liver biopsy showed a pan-acinar hepatitis and extensive cholestasis [10,11]. The fever of that patient persisted even after discontinuation of the drug. However, it was not obvious that prolonged fever could not be differentiated whether the fever of our case that continued until the third day of cefotaxime therapy was related to acute upper respiratory tract infection or a drug induced fever.

In our case, the elevation of liver enzymes, pancytopenia, and the deterioration of bleeding and clotting tests and of renal functions suggested a progressive destructive effect. It was likely that the bone marrow biopsy performed under fresh frozen plasma and thrombocyte replacement has triggered the coagulation disorder or disseminated intravascular coagulation (DIC) once again. DIC and hemorrhage were reported to be the main causes of mortality associated with bone marrow biopsy. Bone marrow biopsy related mortality was reported to be two in 13,506 procedures and one in 54 890 biopsies in the studies [4]. Even if the pain was the most reported complication due to bone marrow biopsy, hemorrhage is most severe complication. Potential risk factors were reported to be associated with bleeding were myeloproliferative disorders, aspirin and warfarin therapy, disseminated intravascular coagulation, and obesity [11]. Prolonged clotting tests and thrombocytopenia might cause a hemorrhage after biopsy, even if replacement was performed. It should be cautious to perform a bone marrow biopsy, if a patient presents with pancytopenia, elevated liver enzymes, and fever and without an abnormality in his peripheral smear [11].

Conclusion

Dexketoprofen and cephalexin, which are commonly prescribed to treat acute respiratory tract infections together at ambulatory or emergency clinics, may cause a life-threatening side effect, such as pancytopenia and acute liver injury. Patients should be informed regarding those rare side effects. Medication should be questioned by the physicians certainly, in case a patient is admitted with elevated liver enzymes and pancytopenia. Invasive procedures, such as bone marrow biopsy should be postponed, until a hematological disease is strongly suspected in the context with laboratory and clinical findings. Discontinuation of drugs and supportive care are essential in the follow-up of patients.

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