



Ceftriaxone-induced toxic hepatitis

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Abstract

Toxic hepatitis or drug-induced liver injury encompasses a spectrum of clinical disease ranging from mild biochemical abnormalities to acute liver failure. The advantages of a long half-life, wide spectrum, high tissue penetration rate, and a good safety profile, make ceftriaxone, a third-generation cephalosporin, a frequent choice in the treatment of childhood infections. Previous studies have reported a few cases of high aspartate aminotransferase and alanine aminotransferase levels, along with three cases of hepatitis caused by ceftriaxone. Here, we report a case of drug-induced toxic hepatitis in a patient who was treated with ceftriaxone for acute tonsillitis.

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INTRODUCTION

Toxic hepatitis or drug-induced liver injury encompasses a spectrum of clinical disease ranging from mild biochemical abnormalities to acute liver failure. The majority of adverse liver reactions are idiosyncratic, and occur in most instances 5-90 d after the causative medication was last taken^[1]. The advantages of a long half-life, wide spectrum, high tissue penetration rate, and a good safety profile, make ceftriaxone, a third-generation cephalosporin, a frequent choice in the treatment of childhood infections. It is excreted mainly by the kidneys, and 35%-45% of the drug is excreted through the bile without being metabolized^[2]. Previous studies have reported a few cases of high aspartate aminotransferase (ALT) and alanine aminotransferase (AST) levels, along with three cases of hepatitis caused by ceftriaxone^[2-4]. Here, we report a case of drug-induced toxic hepatitis in a patient who was treated with ceftriaxone for acute tonsillitis.

CASE REPORT

A 12-year-old boy was admitted with complaints of weakness and fatigue. His personal history revealed treatment with ceftriaxone 50 mg/kg per day, 6 d previously, for tonsillitis. The patient stated that the weakness had begun on the third day of ceftriaxone therapy. He had no chronic disease and had not had contact with anyone with hepatitis. He had not used any drugs, including analgesics and anti-inflammatory drugs, in the previous 6 mo. He had never undergone a blood transfusion or any previous operations, or tooth extraction in the previous year. He had no history of traveling. He was a student in the 6th grade of primary school. He stated that there was no change of color in his feces or urine. During this period, other medications, including herbal remedies and vitamins had not been used. The only drug he had used was ceftriaxone. His liver function tests were at normal levels in the past 2 mo. Physical examination revealed a weight of 43 kg (50 percentile), and a height of 152 cm (50-75 percentile). His general appearance was moderate and seemed weak, and his pharynx was slightly hyperemic. No additional sounds or murmurs were detected upon cardiac and pulmonary examinations. The liver and the spleen were

non-palpable. The neurological examination was normal, along with all the other systems.

Laboratory examination revealed: AST, 819 IU/L (normal range, 10-40 IU/L); ALT, 871 IU/L (normal range, 13-40 IU/L); γ glutamyl transferase (GGT), 285 U/L (normal range, 9-50 IU/L); alkaline phosphatase (ALP), 143 IU/L (normal range, 40-140 IU/L); total bilirubin, 4.2 mg/dL; and direct bilirubin, 2.8 mg/dL. Total protein, albumin, globulin, lactate dehydrogenase, amylase and fasting blood glucose levels were normal. The complete blood count revealed a normal number of leukocytes, erythrocytes and platelets. Peripheral blood smear revealed 60% neutrophils, 30% lymphocytes, 8% eosinophils, and 2% monocytes. The erythrocyte morphology was normal with no atypical cells. Urine analysis, prothrombin time and activated partial thromboplastin time were all in the normal range. Antistreptolysin O titer was 340 TU/mL. Serum iron, iron binding capacity, ferritin, ceruloplasmin, free T3, free T4 and thyroid stimulating hormone levels were also in the normal range. Hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis C virus, anti-hepatitis A virus IgM, anti-hepatitis E virus, cytomegalovirus IgM, and Epstein-Barr virus viral capsid antigen values were negative, whereas anti-HBsAg was positive. Values for IgG, IgM and IgA levels were normal but the value for IgE was 523 IU (normal range 0-100). Anti-nuclear antibody (ANA) and anti-mitochondrial antibody (AMA) were negative. Blood, urine and throat cultures were negative.

Ultrasonography showed minimal enlarged liver size but with normal parenchyma, and gallbladder was normal. The clinical appearance of the patient did not show any signs of cholelithiasis. Evaluating personal history, physical examination and the laboratory findings together, we made a diagnosis of ceftriaxone-induced hepatitis. Liver biopsy was planned, but the patient refused. Ceftriaxone administration was ceased immediately. Pulse methylprednisolone administration was begun at 40 mg/kg in the first 3 d, to be followed by 30 mg/kg for 4 d. A proton pump inhibitor was added to the drug regimen. His vital functions were normal. A steroid-induced hyperglycemic attack with the highest value of 240 mg/dL for 2 d was the only adverse effect of the treatment. He was advised to rest for 2 wk without taking any drugs and to have a light diet. At week 4, the biochemical data revealed: ALT, 95 IU/L (13-40); and GGT, 164 IU/L (9-50). Total bilirubin, direct bilirubin, total protein, albumin and other parameters were normal. Control blood biochemistry at week 10 showed GGT of 85 IU/L (9-50), along with normal values of ALT, AST and other parameters.

DISCUSSION

All the factors suspected to be responsible for hepatitis and disturbed liver function tests, such as viral agents, autoimmune disease, cholelithiasis, storage diseases such as Wilson's disease, hemochromatosis, and endocrine

diseases such as hypo- and hyperthyroidism were excluded when we obtained normal values in viral serological tests of ANA, AMA, ferritin, serum iron binding capacity, ceruloplasmin, free T3, free T4, and TSH.

The absence of a specific cause for the elevated liver function tests, including AST, ALT, ALP, GGT, and total and direct bilirubin, such as blood transfusion, recent tooth extraction, surgery, direct contact with a patient with hepatitis, history of traveling or use of any drugs other than ceftriaxone, other medications, including herbal remedies and vitamins, led us to consider ceftriaxone as the responsible agent. The direct correlation with ceftriaxone use could be verified by measurement of drug levels in the serum or by liver biopsy, or the re-use of the drug, in which case elevated transaminase levels would support our diagnosis of ceftriaxone-induced hepatitis. Measurements of the antibody for liver-kidney microsome (anti-LKM) and cytochrome P450 may be useful for demonstrating drug-induced hepatotoxicity^[4]. Re-use of the drug in our patient was out of the question. He also refused a liver biopsy. In our case, serum measurement of anti-LKM was positive but for technical reasons, serum ceftriaxone levels could not be performed. A prominent increase in the levels of GGT suggest a toxic cause^[3].

Development of hepatitis and elevated liver enzymes caused by antibiotics have been reported in the literature^[2-9]. Cephalosporin-induced hepatotoxicity is rarely observed. Common adverse effects are gallstones (cholelithiasis) or bile lumps. Despite the fact that only a few cases of elevated liver enzymes caused by ceftriaxone have been reported^[2-4], only three cases of hepatitis have been reported in the literature^[2-4]. In one of the cases, ceftriaxone was used to treat Lyme's disease, which resulted in serious side effects and elevated liver enzymes, consequently leading to cessation of the drug^[4]. Similar to our case, an interesting normalization in the level of all the enzymes, except GGT, has been reported at 10 wk after drug discontinuation^[4]. Unlike other cases, our patient showed no signs of severe hemolysis. This probably accounted for early recovery of the patient, along with the absence of any life-threatening complications. This was certainly fortuitous for the patient.

In cases of drug-induced hepatitis, the clinical picture of the hepatitis may represent a direct toxic effect, an idiosyncrasy, or a cholestatic reaction^[1,5]. In our case, the eosinophilia in the blood smear and the elevated IgE levels in the serum suggested that hypersensitivity was responsible for the ceftriaxone-induced hepatitis.

In conclusion, the effect of ceftriaxone along with other hepatotoxic drugs should be considered in any case of elevated liver enzymes and hepatitis.

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