

Steroid Induced Hepatotoxicity in an Adolescent with T-Cell Lymphoblastic Lymphoma: Case Report

T-Hücreli Lenfoblastik Lenfomalı Adölesan Bir Hastada Steroid Kullanımına Bağlı Hepatotoksisite

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ABSTRACT Although hepatotoxicity is a quite frequent side effect of chemotherapy in patients with cancer, steroid-induced hepatotoxicity is rare in children. Here we report a 16-year-old boy with precursor T-cell lymphoblastic lymphoma in who hepatomegaly and elevated liver function tests were found after initiation of steroid treatment. All other causes of hepatic dysfunction were excluded and the patient was diagnosed as steroid-induced hepatotoxicity. Hepatomegaly regressed and liver function tests were normalized after discontinuation of steroids. Steroid-induced hepatotoxicity leading to dose reduction during treatment is extremely rare but must be kept in mind in children under chemotherapy when other causes of hepatic dysfunction were excluded.

Key Words: Lymphoma; child; medical oncology

ÖZET Hepatotoksisite, kanserli hastalarda yaygın görülen bir yan etki olmasına rağmen çocuklarda steroide bağlı hepatotoksisite nadir olarak görülmektedir. Bizim olgumuzda 16 yaşında, prekürsör T-hücreli lenfoblastik lenfoma nedeniyle steroid tedavisi alan hastada steroid başlanmasından sonra hepatomegali ve karaciğer fonksiyon testlerindeki yükselmeden bahsedilmiştir. Hepatik disfonksiyonun diğer tüm olası sebepleri ekarte edilmiş ve karaciğer enzimlerindeki yükselme steroide bağlı hepatotoksisite olarak değerlendirilmiştir. Steroid tedavisinin kesilmesi sonrasında hepatomegali gerilemiş ve karaciğer fonksiyon testleri normal seviyelere inmiştir. Tedavi dozunun düşürülmesine yol açan steroide bağlı hepatotoksisite nadir olarak görülmesine rağmen kemoterapi alan çocuk hastalarda hepatik disfonksiyonun diğer nedenleri ekarte edildiğinde akla gelmelidir.

Anahtar Kelimeler: Lenfoma; çocuk; medikal onkoloji

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Hepatotoxicity is a frequent dose-limiting side effect of chemotherapy in children with cancer. Malignant liver infiltration, intercurrent infections or other drugs may also cause elevated liver function tests but steroid-induced hepatotoxicity is very rare in children. Here we report an adolescent with T-cell lymphoblastic lymphoma who had elevated liver function tests during steroid therapy, but had returned to normal levels after tapering the dosage of steroids.

CASE REPORT

A previously healthy 16-year-old boy was admitted to our hospital with sudden complaints of swelling on his face and neck, and difficulty to

breathe. History revealed that he has been incidentally determined to be a hepatitis B virus (HBV) carrier for 3 years without any symptoms. On physical examination, there was orthopnea, venous congestion and edema over his face and neck, but no hepatosplenomegaly. Computed tomography (CT) showed an anterior mediastinal mass of 7,5x10x13,5 cm causing compression of superior vena cava and trachea. Complete blood count, blood chemistry with electrolytes, abdominal ultrasonography and bone marrow aspiration were all normal. Parenchyma of liver was normal showing no infiltration with no hepatomegaly. Echocardiography was performed showing no abnormality in cardiac functions or right cardiac failure due to superior vena cava syndrome. Informed consent was taken from the patient’s parents for treatment and publication of his data before he was started on chemotherapy. The symptoms were rapidly regressed after starting methylprednisolone 30 mg/m²/day with a diagnosis of superior vena cava syndrome. A CT guided biopsy was performed from the mass on the third day of corticosteroid treatment and L1-L2 blasts were seen in imprint cytology. The diagnosis of precursor T-cell lymphoblastic lymphoma was also made based on histopathological and immunohistochemical findings.

The treatment was switched to 60 mg/m²/day prednisolone according to BFM chemotherapy protocol for T cell lymphoblastic lymphoma starting with prednisolone alone until the 8th day on which continuing with vincristine and daunorubisin with prednisolone. On the 5th day of steroid treatment, liver function tests were found to be elevated (AST: 106 U/L, ALT:217 U/L, GGT:55 U/L) with normal total and direct bilirubin levels. The liver was palpable of 5 cm below right lower costal margin with prominent tenderness over the right upper quadrant. No jaundice was observed. The chemotherapy was postponed and he was started on Lamivudine treatment (100 mg/day) soon after blood was withdrawn for hepatitis and other viral markers including TORCH and Epstein Barr virus (EBV), which were all found negative later. Since he was HBV carrier, this was confirmed with lab-

oratory tests of HBsAg (+), Anti HBs (-) and Anti HBc IgM (-), AntiHBc IgG (+), HBV DNA PCR (-), meaning no reactivation of hepatitis B infection. Autoimmune hepatitis was excluded with negative nuclear tests for antinuclear antibodies and liver-kidney microsomal antibodies. Also, there were no clinical findings of Wilson’s disease in addition to normal ceruloplasmin level and normal eye examination which was negative for Kayser-Fleischer ring. Abdominal ultrasound revealed no abnormality in neither bile duct or in intrahepatic and extrahepatic ducts. The prednisolone dose was tapered when ALT and AST were 421U/L and 184 U/L respectively, since all clinical and laboratory examinations revealed no other cause than steroid treatment. AST and ALT levels decreased to 163U/L and 34 U/L respectively after just 4 days which allowed delivering chemotherapy and completely normalized after discontinuation of prednisolone (Figure 1).

DISCUSSION

Hepatotoxicity can occur as a result of many causes such as acetaminophen or non-acetaminophen drugs, metabolic diseases, autoimmune liver disease or infections in children. However, almost half of acute liver failure reasons remain to be undetermined.¹ Hepatotoxicity during chemotherapy are almost always related to cytotoxic agents or to newer targeted treatments; steroids are generally

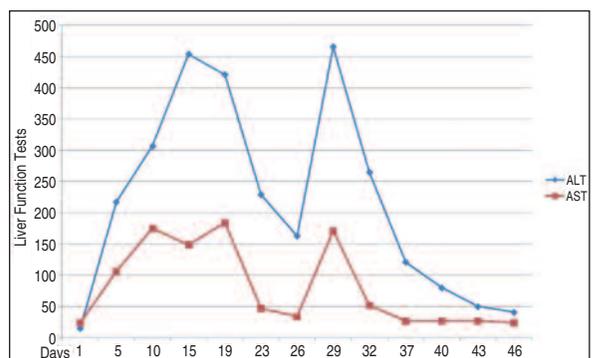


FIGURE 1: Liver Function tests of the patient: Methylprednisolone was started at day 0, the therapy was switched to prednisolone at day 5, steroid dose started to taper at day 15, chemotherapy was started at day 23, and steroid treatment was stopped at day 43.

(See color figure at <http://www.turkiyeklinikleri.com/journal/pediatric-dergisi/1300-0381/>)

considered to be safe drugs with regard to hepatotoxicity and they can even be used for treatment of severe hepatitis cases.² In a recent report of Gupta et al, tyrosine kinase inhibitor-imatinib induced hepatotoxicity in a 20 year-old with chronic lymphoblastic leukemia (CML) was successfully treated with oral prednisone therapy.³

On the other hand, a review of the literature shows that steroids are not entirely safe for the liver. Rare case reports of corticosteroid hepatotoxicity indicate usually high dose, pulse steroid treatment during multiple sclerosis and optic neuritis, especially in adults.⁴⁻⁸ In all cases, possible causes of hepatotoxicity were excluded and liver function tests were normalized after cessation of steroids. In a recent study, increased individual glucocorticoid sensitivity due to the N363S polymorphism has been found to be a predisposing factor to hepatotoxicity during high-dose steroid therapy for Acute Lymphoblastic Leukaemia (ALL).⁹ The authors report 31.3% and 11.1% hepatotoxicity during ALL therapy among carriers and non-carriers of N363S mutation, respectively. Unfortunately, this test was not available for our patient.

The awareness and early recognition of hepatotoxicity is critical as the severity of the disease can range from asymptomatic transient liver function tests abnormalities up to acute hepatitis, and even to fulminant liver failure and death.^{6,8} Hepatotoxic reactions usually appear without any previous condition, and are determined by individual susceptibility.¹⁰ Steroid-induced hepatotoxicity was thought to result from several mechanisms such as reactivation of viral infections, steatosis-steatohepatitis or immune-allergic hepatitis, or auto-immune hepatitis.⁶ Despite their anti-inflammatory and anti-allergic properties, steroids may trigger immunoallergic hepatitis.⁸ Although the exact mechanism of

hepatotoxicity is not known, it is also most likely to be because of idiosyncratic reaction of steroids and their metabolites.² There are two types of idiosyncrasy; immunoallergic and metabolic (nonallergic). In metabolic idiosyncratic drug induced hepatotoxicity, the liver injury is thought to be caused by aberrant hepatic metabolism leading to overproduction of reactive metabolites, considered to be unpredictable and usually dose-dependent.⁴ Clinical case reports of hepatotoxicity related to methylprednisolone and prednisolone are uncommon despite the extended use of them in clinical practice in many areas of medicine.⁶ It is quite important to keep in mind the hepatotoxicity and to think about withdrawal of the drug in time to avoid unnecessary interventions.

Our patient was an adolescent with elevated liver enzymes and we checked all serological tests for autoimmune hepatitis; viral hepatitis such as cytomegalovirus (CMV) and EBV; reactivation of hepatitis B virus; other hepatic viruses hepatitis A virus (HAV) and hepatitis C virus (HCV); and Wilson's disease with all negative results. There were also no sign of malignant infiltration nor cardiac failure due to superior vena cava syndrome. So we have excluded all other possible causes of liver function tests abnormalities. Hepatomegaly regressed and liver function tests returned to normal after cessation of prednisolone. During the treatment according to the protocol, after starting with steroids, liver function tests were elevated again with no hepatomegaly or reactivation of hepatitis B or no documented viral infections. After discontinuation of steroids, his liver function tests did not rise again, since he has been followed in remission with maintenance treatment according to the protocol. This rare condition must be kept in mind in patients with elevated liver enzymes when all other causes were excluded.

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