

Development of fatty liver in children with non-Hodgkin lymphoma

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The aim of this study is to investigate the development of hepatosteatosi in children with non-Hodgkin lymphoma. Twenty-eight patients were evaluated retrospectively for hepatosteatosi by computed tomography. Mild, moderate and severe hepatosteatosi were defined as the difference between the average liver attenuation and the average spleen attenuation, equaling (- 10) - (- 19); (- 20) - (- 29); and ≥ 30 HU, respectively. "Vaguely" and "obvious" hepatosteatosi were defined as none or mild hepatosteatosi, and moderate and severe hepatosteatosi, respectively. In T-cell lymphoma, obvious hepatosteatosi was determined in 1 of 12 patients (8.3%) at the first evaluation, 8 of 12 patients (66.7%) at the second evaluation and 4 of 12 patients (33.3%) at the third evaluation. In B-cell lymphoma, obvious hepatosteatosi was determined in none of 16 patients at the first evaluation, 2 of 16 patients (12%) at the second evaluation and none of the patients at the third evaluation. In the second evaluation, severe high serum total cholesterol and triglyceride levels were determined in 4 of 5 patients. We observed higher fatty liver ratios, and high triglyceride and cholesterol levels, although the data were obtained from a small number of patients.

Key words: children, fatty liver, lymphoma, non-Hodgkin.

Drugs are an important cause of liver injury. Manifestations of hepatotoxicity due to drugs are highly variable, ranging from asymptomatic elevation of hepatic function tests to fulminant hepatic failure. Physicians should be watchful in identifying drug-induced hepatotoxicity, because early detection can decrease the severity of hepatotoxicity if the drug is discontinued¹.

It is well known that different chemotherapeutic agents, including alkylating agents, nitrosoureas, antimetabolites, antitumor antibiotics, tubulin-acting agents and others (such as irinotecan, platinum derivatives, asparaginase, etc.), can cause damage to the liver².

L-asparaginase has become an important component of the treatment of both childhood acute lymphoblastic leukemia and lymphoma. It depletes asparagine—a nonessential amino acid which many cells depend on for normal metabolic processes—in the blood. There are, however, some side effects, including

type 1 hypersensitivity reactions such as cutaneous rashes, hypertriglyceridemia, hypoalbuminemia, coagulopathy, hyperglycemia and thromboembolic events^{3,4}.

Lipid metabolism abnormalities, including hypo-/hypercholesterolemia and/or hypo-/hypertriglyceridemia have been described in patients who received L-asparaginase previously⁵. The effects of L-asparaginase and/or other chemotherapeutic agents on lipid metabolism have been associated with alterations in lipid synthesis and clearance⁵.

Deficiency or imbalance of amino acids, or some agents such as ethionine, tetracycline and ethanol, can also produce fatty liver. Our knowledge about the production of fatty liver by L-asparaginase is very limited⁶.

The aim of this study is to investigate the development of fatty liver in children with non-Hodgkin lymphoma (NHL).

Material and Methods

A total of 28 patients with NHL who were seen at our institution between 2006 and 2012 were evaluated retrospectively for demographic characteristics, laboratory findings and radiological features. Patients with B-cell lymphoma and T-cell lymphoma were treated according to the BFM-95 protocol⁷ and the BFM T-cell lymphoma protocol⁸.

Abdominal tomography (CT) examinations were performed for B-cell NHL at diagnosis (the first evaluation), after the first CC course (the second evaluation) and after the second BB or CC course (the third evaluation). For T-cell lymphoma, they were performed at diagnosis (the first evaluation), the 33rd day of induction therapy (the second evaluation), and after reinduction (the third evaluation).

Abdominal CT examinations were performed with a 4-detector CT scanner (Aquilion 4 detector; Toshiba, Tokyo, Japan), with voltage of 100-120 kVp and tube current of 100-250 mAs; images were obtained in the craniocaudal direction. Water-soluble oral contrast agents of between 750-1500 ml (2%) were consumed 1 hour before the examinations. 1-2 ml/kg of non-ionic contrast medium with 300 mg/ml iodine concentration was injected at a flow rate of 2-3 ml/s, followed by a 50-ml saline chaser with the same flow rate. The scan was started after 70 s delay and obtained on portal phase. All images were reconstructed as 3 mm axial sections and sent to the picture archiving and communication systems (PACS). Stored image data sets in the PACS were analyzed by two radiologists, who were blinded to definitive diagnosis, to determine the degree of hepatic steatosis at diagnosis and follow-up.

Attenuation values of right hepatic lobe segments (segments V, VI, VII and VIII), which were divided anatomically from each other according to Couinaud's system, and upper, middle and lower thirds of the spleen were measured using a 15 mm² circular region of interest (ROI). The ROI was placed within the hepatic and splenic parenchyma, which does not contain macroscopic vessels or any focal lesions on portal phase contrast-enhanced images. Average hepatic and splenic attenuation measurements were calculated and the mean liver attenuation value then subtracted from the mean spleen attenuation value. Mild, moderate

and severe hepatosteatoses were defined as the difference between the average liver attenuation and the average spleen attenuation, equal to -10 HU - -19 HU, -20 HU - -29 HU, and \geq 30 HU, respectively (Fig. 1a-d).

No hepatosteatoses and mild hepatosteatoses were defined as "vaguely hepatosteatoses"; and moderate and severe hepatosteatoses were defined as "obvious hepatosteatoses."

Results

Twenty-eight patients, 20 males and 8 females, with a median age of 11 (range, 1 to 17 years), were diagnosed as NHL between 2006 and 2012. Twenty-four patients had stage III, 3 patients had stage IV and one patient had stage II disease. Sixteen patients (57%) had high-grade B-cell lymphoma, and 12 patients (43%) had T-cell lymphoma.

Among those with T-cell lymphoma, 1 of 12 patients (8.3%) had mild hepatosteatoses at the first evaluation; 2 of 12 patients (16.7%) had mild, 2 of 12 patients (16.7%) had moderate and 6 of 12 patients (50%) had severe hepatosteatoses at the second evaluation; and 2 of 12 patients (16.7%) had mild and 4 of 12 patients (33.3%) had moderate hepatosteatoses at the third evaluation.

Among those with B-cell lymphoma, 4 of 16 patients (25%) had mild hepatosteatoses at the first evaluation; 7 of 16 patients (44%) had mild and 2 of 16 patients (12%) had moderate hepatosteatoses at the second evaluation; and 8 of 16 patients (50%) had mild and 2 of 16 patients (12%) had moderate hepatosteatoses at the third evaluation.

In patients with T-cell lymphoma, obvious hepatosteatoses was determined in 1 of 12 patients (8.3%) at the first evaluation, 8 of 12 patients (66.7%) at the second evaluation and 4 of 12 patients (33.3%) at the third evaluation. In those with B-cell lymphoma, obvious hepatosteatoses was determined in none of 16 patients at the first evaluation, 2 of 16 patients (12%) at the second evaluation and none of the patients at the third evaluation. When values of both groups were compared, p values were determined as >0.05 , 0.005 and 0.024 for the first, second and third evaluations respectively.

Serum lipid profiles of 5 of the 12 patients with T-cell lymphoma were obtained from their

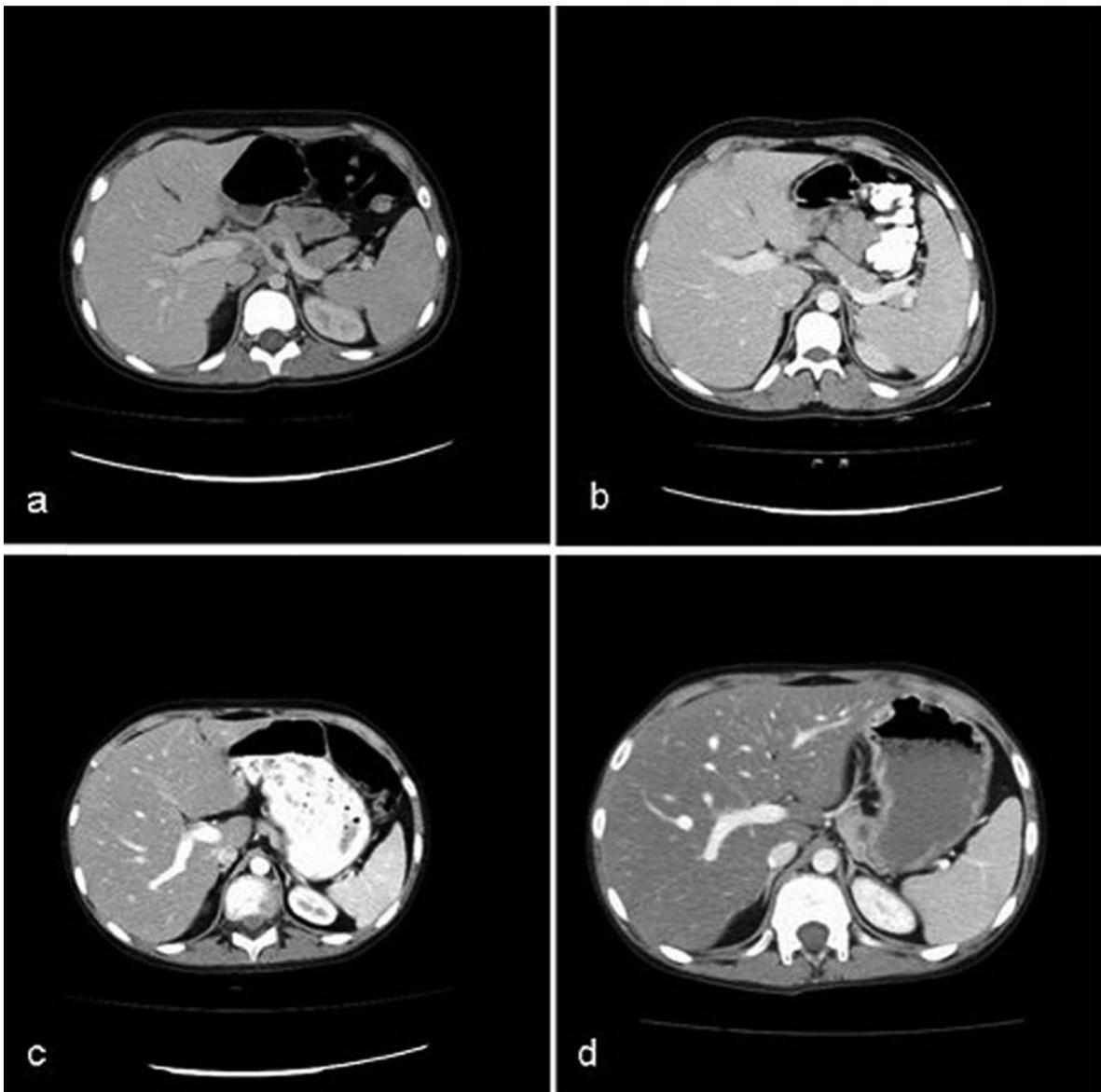


Fig. 1(a-d.) Hepatosteatosi grades of patients, as shown by computed tomography

hospital charts. In the second evaluation, severe high serum total cholesterol and triglyceride levels were determined in 4 of the 5 patients (Fig. 2). Serum triglyceride and total cholesterol levels ranged from 81 to 3605 mg/dl (median 1065 mg/dl) and 131 to 799 mg/dl (median 258 mg/dl) respectively. Due to high triglyceride levels, gemfibrozil was started in two patients. Lipid profiles of the patients were within normal limits at the third evaluation.

Four patients in this group were lost in due course because of progressive illness. However, it was observed that the lipid profiles of all

patients returned to normal in the follow-ups.

Discussion

In drug-induced hepatotoxicity, initial hepatic injury following drug administration is due to direct cell stress, direct mitochondrial inhibition and/or specific immune reactions at the first step. After this, the initial injury can lead to mitochondrial permeability transition, and finally to necrosis or apoptosis⁹.

Patterns of drug-induced hepatotoxicity are zonal necrosis, hepatitis, cholestasis, steatosis, granuloma, vascular lesions and neoplasms¹⁰.

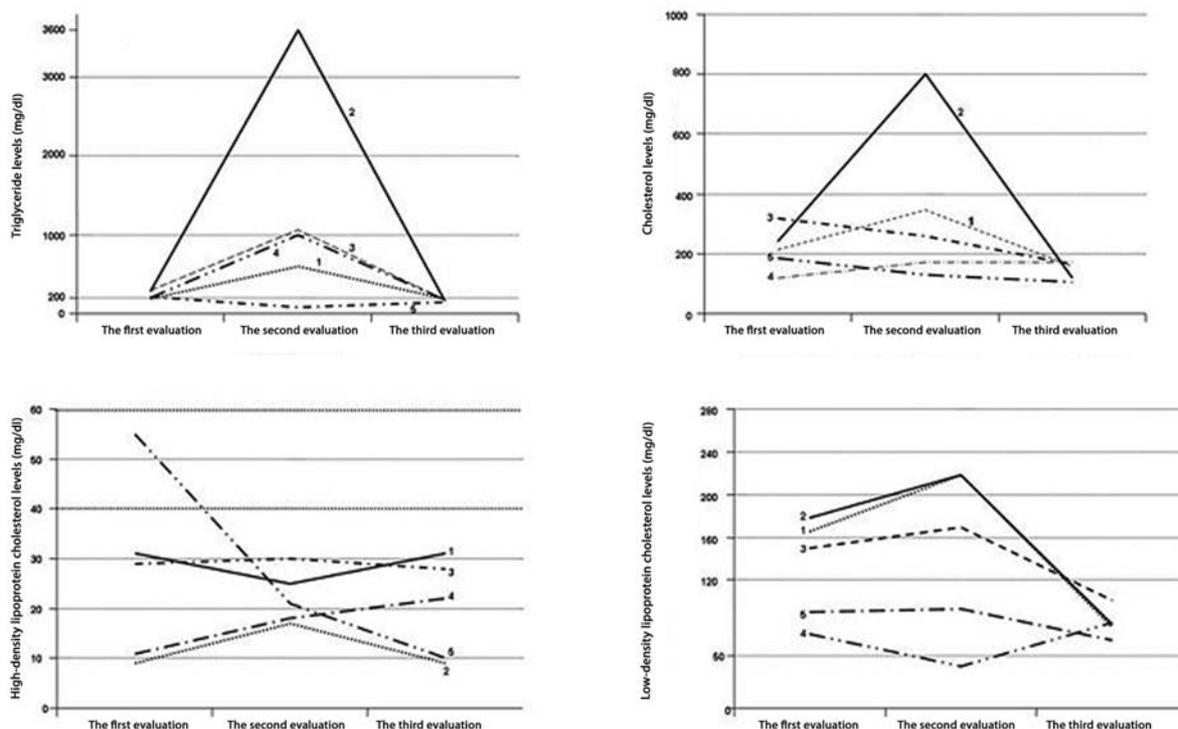


Fig. 2. Patients' triglyceride, total cholesterol, high-density lipoprotein and low-density lipoprotein levels

Various chemotherapeutic agents can cause damage to the liver². In this study, we aimed to investigate the development of fatty liver in children with NHL using CT. Major drugs for T-cell lymphoma⁷ and major drugs for B-cell lymphoma⁸ were used. The drugs are similar, with the exception of L-asparaginase, 6-mercaptopurine and 6-thioguanine, which are used in T-cell lymphoma.

In our study, obvious hepatosteatorosis was determined in 8.3%, 66.7% and 33.3% of the patients with T-cell lymphoma at the first, second and third evaluations respectively. In B-cell lymphoma, obvious hepatosteatorosis was determined in 0%, 12% and 0% of the patients at the first, second and third evaluations respectively.

L-asparaginase is one of the main drugs used for acute lymphoblastic leukemia and T-cell lymphoma. It hydrolyzes L-asparagine in the serum, after which depletion of L-asparagine results in the death of acute lymphoblastic leukemia and T-cell lymphoma cells. Hepatic toxicity due to L-asparaginase is quite frequent, and its mechanism is uncertain. The probable mechanism of hepatotoxicity due

to L-asparaginase involves impaired protein synthesis due to asparagine depletion. This hepatotoxicity is characterized by moderate reversible elevation of aminotransferase, bilirubin, and/or alkaline phosphatase. Hyperammonemia may develop as asparagine is broken down². In patients in whom L-asparaginase has been used, hepatosteatorosis, likely due to decreased lipoprotein synthesis, can be seen. It is found at autopsy in 42-87% of treated patients¹¹.

In our study, obvious hepatosteatorosis in patients with T-cell lymphoma during the second evaluation period (33rd day of induction therapy) occurs at the end of eighth dose of L-asparaginase therapy. The main difference between the therapy of these patients and that of B-cell lymphoma patients is the use of L-asparaginase. For this reason, obvious hepatosteatorosis is thought to be related to L-asparaginase therapy. The high rate of obvious hepatosteatorosis in patients with T-cell lymphoma in the third evaluation (after reinduction therapy) was also thought to be related to the 4 doses of L-asparaginase used in reinduction therapy. But while the

rate of obvious hepatosteatosis in the second evaluation was 66.7%, the rate in the third evaluation was 33.3%. These differences can be explained on the basis of the different doses of L-asparaginase (eight doses in induction therapy and four doses in reinduction therapy), and the different timing of the evaluation after the last L-asparaginase dose (the third evaluation took place after the 31st day of the last L-asparaginase dose in reinduction therapy).

In children with cancer, lipid abnormalities due to altered nutritional states or altered lipid metabolism and reduced levels of lipoprotein and elevated triglycerides suggest that L-asparaginase-specific alterations have occurred¹². Severe complications, including acute pancreatitis and neurologic complications such as peripheral neuropathy and intermittent central nervous system symptoms due to elevated triglyceride levels, have been recognized. Children with high triglycerides can be treated with fasting, intravenous fluids, low doses of fibrates or plasmapheresis^{13,14}. Serum lipid profiles of 5 patients with T-cell lymphoma were obtained from their hospital charts. In the second evaluation, severe high serum total cholesterol and triglyceride levels were found in 4 of the 5 patients. Lipid profiles of the patients were within normal limits at the third evaluation. In two of our patients, gemfibrozil was started due to high triglyceride levels.

In conclusion, in patients who underwent L-asparaginase treatment, increases in triglyceride and cholesterol levels and in fatty liver ratios were observed, although the data was derived from a small number of patients. We want to emphasize the rate of occurrence of fatty liver and the importance of routine lipid-level evaluation in children with NHL whose chemotherapy regimens contain L-asparaginase.

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