HEMATOONKOLOJİDE YAĞLI KARACİĞER

(HEMATOLOJİK MALİGNİTELERDE KEMOTERAPİ SONRASI YAĞLI KARACİĞER HASTALIĞI)

FATTY LIVER IN HEMATOONCOLOGY

(FATTY LIVER DISEASE AFTER CHEMOTHERAPY IN HEMATOLOGIC MALIGNANCIES)

Raim Iliaz[1], Filiz Akyuz[2], Aslı Ormeci[2], Umit Akyuz[3], Kadir Demir[2], Fatih Besisik[2], Mine Gulluoglu[4], Sabahattin Kaymakoglu[2]

ÖZET

Kemoterapi ile ilişkili yağlı karaciğer hastalığı, basit steatozdan steatohepatite kadar değişen yağlı karaciğer hastalıklarının spektrumudur. Kemoterapiye bağlı yağlanma ile ilgili çalışmaların çoğu kolorektal kanserli hastalar üzerindedir. Hematolojik maligniteleri olan hastalarda kemoterapiye bağlı hepatosteatoz vakası bildirilmemiştir. Amacımız bu malignite grubunda kemoterapiye bağlı hepatosteatozları değerlendirmektir. Yöntemler: Bu çalışmaya hematolojik malignite nedeniyle kemoterapi alan, karaciğer enzimleri sürekli yüksek olan ve karaciğer biyopsisi yapılan toplam 11 hasta dahil edildi. Tüm hastalar biyopsi öncesi yüksek karaciğer enzimlerinin virolojik ve toksik etiyolojileri açısından değerlendirildi. Tespit edilebilir etiyolojileri olan hastalar çalışma dışı bırakıldı. Karaciğer biyopsisi yapılan hastalar çalışmaya dahil edildi. Bu hastalar Hastaların biyopsileri hepatolojide uzmanlaşmış tek bir patolog tarafından yapılmıştır. Hepatik steatoz, Brunt sınıflamasına göre derecelendirildi. Bulgular: Hastaların ortalama yaşı 35.8±13.5 yıl idi. Hastaların sekizi (%72.7) erkek, 3'ü (%27.3) kadındı. Çalışmamızın sonuçlarına göre 6 hastanın (%54,5) karaciğer biyopsisinde hepatosteatoz mevcutken, 5 (%45,5) hastada steatoz yoktu. Hepatosteatoz olan ve olmayan gruplar yaş(35 ± 9vs.40 ± 18 yıl)(p=0.57) ve cinsiyet (p=0.55) açısından benzerdi. Hepatosteatozlu hastaların vücut kitle indeksi, steatoz olmayan gruba göre daha yüksekti (27,8±4kg/m2'ye karşı 21.6±3kg/m2)(p=0,02). Hepatosteatoz olan ve olmayan hastalarda glukoz, kolesterol ve trigliseritler istatistiksel olarak benzerdi. Sonuç: Hematolojik malignite tedavisi alan hastalarda kemoterapiye bağlı hepatosteatoz insidansı yüksek bulundu. Karaciğer fonksiyonunun kontrolü için remisyon döneminde takip önemlidir

Anahtar kelimeler: kemoterapi ile ilişkili hepatosteatoz, hematolojik maligniteler, alkolsüz yağlı karaciğer hastalığı

[1] *Atlas University, Medical Faculty, Department of Gastroenterology, Istanbul-Turkey*
[2] *Istanbul University, Istanbul Medical Faculty, Department of Gastroenterology, Istanbul-Turkey*
[3] *Yeditepe University Hospital, Department of Gastroenterohepatology, Istanbul-Turkey*
[4] *Istanbul University, Istanbul Medical Faculty, Department of Pathology, Istanbul-Turkey*

ABSTRACT

Objective: *Chemotherapy-associated fatty liver disease is the spectrum of fatty liver diseases ranging from simple steatosis to steatohepatitis. The majority of studies about chemotherapy-associated steatosis are on the patients with colorectal cancer. There is no reported case of chemotherapy associated hepatosteatosis in patients with hematological malignancies. Our aim is to evaluate chemotherapy associated hepatosteatosis in this malignancy group. Methods: In this study we included a total of 11 patients who had received chemotherapy for hematological malignancy, had persistently elevated liver enzymes and perform liver biopsies. All patients evaluated before biopsy for virologic and toxic etiologies of elevated liver enzymes. Patients with detectable etiologies were excluded from study. Patients who performed liver biopsy were included in the study. These patients Patients' biopsies were evaluated by a single pathologist who is specialized in hepatology. Hepatic steatosis was graded according to the classification of Brunt. Results: The mean age of patients was 35.8±13.5 years. Eight(72.7%) patients were male and 3(27.3%) were female. According to the results of our study, hepatosteatosis was present in the liver biopsies of 6 patients(54.5%), but in five(45.5%) patients, there were no steatosis. The groups with and without hepatosteatosis were similar in terms of age(35 ± 9vs.40 ± 18 years)(p =0.57) and sex (p=0.55). Body mass index of the patients with hepatosteatosis were higher compared with the group with no steatosis(27.8±4kg/m2 vs 21.6±3kg/m2)(p = 0.02). Glucose, cholesterol and triglycerides in patients with and without hepatosteatosis were statistically similar. Conclusion: Incidence of chemotherapy associated hepatosteatosis was found to be high in patients receiving treatment for hematologic malignancies. Follow-up is important during the remission period for the control of liver function.*

Key words: *chemotherapy associated hepatosteatosis, hematologic malignancies, nonalcoholic fatty liver disease*

INTRODUCTION

The drugs used in the oncological treatment are increasing rapidly as a result of studies in recent years. However, the increase in chemotherapy associated liver injury reported in recent studies is also remarkable. Chemotherapy associated liver injuries include hepatic steatosis, steatohepatitis and sinusoidal injury (1,2). Nonalcoholic fatty liver disease (NAFLD) is a spectrum of changes associated with fat accumulation in hepatocytes. NAFLD is a hepatic manifestation of insulin resistance and is a part of the metabolic syndrome (3,4). Recently, some studies showed that the prevalence of NAFLD is higher in patients receiving chemotherapy compared with the patients not receiving chemotherapy. These findings introduced the entity of the fatty liver disease associated with chemotherapy (5). Chemotherapy-associated fatty liver disease is the spectrum of the fatty liver diseases ranging from simple steatosis to steatohepatitis (6). The majority of studies about chemotherapy-associated steatosis are on the patients with colorectal cancer. All of these patients received neoadjuvant chemotherapy and hepatic resection due to liver metastases. There is not any report on hepatic steatosis associated with chemotherapeutic agents used in the treatment of hematological malignancies. The aim of our study is to determine the etiology of liver damage and evaluate the presence of chemotherapy associated liver disease in patients with high aminotransferase levels beside receiving chemotherapy for hematological malignancies.

METHODS

Patients and Method

In our study, a total of 11 patients who underwent liver biopsy in our department evaluated retrospectively. These patients had receivedchemotherapy for hematological malignancy and were in remission clinically. Chemotherapy ended at least 3 months before the liver biopsies. Also exclude patients with recently exposed to hepatotoxic substaces. Patients have negative viral serology (HBsAg, AntiHCV). Abdominal ultrasound and/or computed tomography performed to all patients to exclute macroscopic bile tract pathologies also intrahepatic mass lesions. There was no pathology in imaging technics to explain the liver enzyme elevation. Due to the persistent and unexplained high aminotransferase levels, we decided to do liver biopsy. Informed consent was taken from all patients before the liver biopsy. Patiens with chronic alcohol use, uncontrolled diabetes, patients receiving therapy for hyperlipidemia and morbid obese patients were excluded. In order to obtain a standard in evaluation of liver biopsy materials, patients' biopsies were evaluated by a single pathologist who is specialized in hepatology. Hepatic steatosis was graded according to the classification of Brunt. Informed consent was obtained from all patients in the study. Our study has been approved by the local academic board.

Statistical Analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) (IBM, New York, United States) software package program. Descriptive values were given as mean and standard deviation. Categorical variables were expressed as the number of cases and the percentage value. Continuous variables were analyzed using Kolmogorov-Smirnov and Shapiro Wilk tests to determine whether there was normal distribution. The Student's t-test and Mann-Whitney-U test were used depending on the variables' situation i.e. normally distributed or not. Statistical significance was set as $p < 0.05$.

RESULTS

The study enrolled 11 patients and the mean age was 35.8 ± 13.5 years. Eight (72.7%) patients were male and 3 (27.3%) were female. In total of 11 patients, the hematological malignancies were acute lymphoblastic leukemia (ALL) in 6 patients, acute myeloid leukemia(AML)in 2 patients, chronic lymphocytic leukemia (CLL) in 2 patients, and non-Hodgkin's lymphoma (NHL) in 1 patient. Patiens were followed by the Department of Hematology and were in remission clincally. All patients received L-asparaginase and alkylating agents in common due to the hematologic malignancies they had. Six patients had received steroid therapy in addition. According to the results of our study, hepatosteatosis was present in the liver biopsies of 6 patients (54.5%), and there was no steatosis in the other five (45.5%) patients.

In 5 of the patients with hepatosteatosis (n=6), there were grade 3 hepatosteatosis in pathological examination. The rate of steatosis was 90% in two patients, 80% in two patients, and 70% in one patient. The sixth patient had grade 1 hepatosteatosis with 30% steatosis. In patients without hepatosteatosis, histological findings were consistent with chronic hepatitis in 3 patients, blastic cell infiltration in 1 patient and ground-glass opacity in the hepatocytes in 1 patient's biopsy material. Patients in the study were divided into two groups according to the presence of hepatosteatosis. The groups with and without hepatosteatosis were similar in terms of age (35± 9 years vs 40 ± 18 years)(p = 0.57) and sex (p = 0.55). Glucose values were similar in the two groups(p = 0.94). Between groups with and without hepatosteatosis, total leukocyte count (6840/mL vs 8735/mL)(p = 0.49), hemoglobin (12g/dL vs 10 g/dL)(p = 0.36), platelets (188,200/mm3 vs 246,400/mm3)(p = 0.43), and albumin (3.34 g/dL vs 3.72 g/dL)(p = 0.42) values were found to be similar. Body mass index of patients with hepatosteatosis was higher as compared with patients without fatty liver (27.8 ± 4kg/m2 vs 21.6 ±3kg/m2) (p = 0.02). Alanine aminotransferase levels in 6 patients with hepatosteatosis were slightly higher compared with patients without steatosis, but the elevation was away from reaching statistical significance (137 ± 83 IU/L vs 108 ± 88 IU/L)(p = 0.59). In patients with hepatosteatosis, ?-glutamyl transpeptidase (254 ± 223 IU/L vs 109 ± 48 IU/L) (p = 0.18) levels were higher than the other group. But, there was no statistically significant difference between two groups. Cholesterol (194 ± 37 mg/dL vs 164 ± 50 mg / dL)(p = 0.28) and triglycerides (198 ± 91 mg/dL vs 118 ± 52 mg / dL)(p = 0.14) levels were also higher in patients with hepatosteatosis. Besides that, levels in both groups were statistically similar. Detailed results of all patients enrolled in the study and subgroups based on the hepatosteatosis can be seen in table 1.

Table Legend:

Table 1: Characteristics of patients with and without hepatic steatosis

	Total (n= 11)	With hepatosteatosis (n= 6)	Without hepatosteatosis (n= 5)	P value
Age (years)	35±13	35±9	40±18	0.57
Sex (M/F)	8/3	5/1	3/2	0.55
BMI (kg/m²)	28±4.5	28±4	22±3	**0.02**
Glucose (mg/dl)	96±24	97±30	98±17	0.94
AST (IU/L)	87±89	85±40	94±125	0.87
ALT (IU/L)	132±83	137±83	108±88	0.59
GGT (IU/L)	195±185	254±223	109±48	0.18
Cholesterol (mg/dl)	178±41	194±37	164±50	0.28
Triglycerides (mg/dl)	158±81	198±91	118±52	0.14

BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: ɣ-glutamyl transpeptidase

DISCUSSION

Chemotherapy-associated steatosis has been put forward in recent reports, particularly in patients with colorectal cancer who underwent hepatic resection after neoadjuvant therapy. There is no information in the literature about chemotherapy associated steatosis after chemotherapeutic regimens for non-colorectal cancer. In our study, 6 of 11 (54.5%) patients who have received L-asparaginase chemotherapy with alkylating agents due to hematological malignancies had hepatosteatosis. In 5 of these patients hepatosteatosis were found to be severe.

In a study of Zeiss et al showed that patients who received floxurid therapy by hepatic artery infusion pump due to metastatic colorectal malignancy developed hepatosteatosis proven by the evaluation of liver resection materials (7). In another study, there were changes compatible with fatty liver disease by computed tomography in 47% of 27 patients with colorectal malignancy who received 5-FU and folinic acid therapy (8). However, there was no histological verification in this study. Hepatosteatosis was determined only by radiological methods. In our study, although the number of patients is low, hepatosteatosis was observed in 54.5% of patients shown by a liver biopsy. In patients with oncological diseases, it is not always possible to do liver biopsy because of other co-morbidities and poor general health of patients. Therefore, an assessment was made retrospectively in our study.

Age is known as a risk factor in drug-induced liver injury. The risky age varies depending on the drug used. For example, while being old is a risk factor for isoniazid damage, young age possesses more risk for the damage associated with aspirin (9). Drug-induced liver injury has been reported more frequently in women (10). In contrast, patients with and without hepatosteatosis did not differ in age and sex in our study.

There is a close relationship between NAFLD and type 2 diabetes mellitus and also with hyperglycemia (11). However, there was no difference between blood glucose values of two groups in our study. This result suggests that glucose levels were not effective in chemotherapy-related hepatic steatosis. However, due to our small number of patients, it is not possible to make a definitive judgement.

Ninety-five patients with hyperlipidemia were evaluated by Assy et al and NAFLD was detected in 50% of these patients by ultrasonography. However, there was no histological verification in these patients. As a result of this study, Assy et al commented that hyperlipidemia is usually associated with hepatic steatosis (12). Also, studies defending lipid-lowering drugs for treating NAFLD support the relationship between hyperlipidemia and NAFLD (13). In addition, some chemotherapeutic agents are known to increase the levels of lipids (such as vincristine). In our study, the level of cholesterol and triglycerides in patients with hepatic steatosis were higher than in the patients without steatosis. But these differences were not statistically significant.

Liver enzyme alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) are well known markers of liver injury (14). Many studies showed that ALT was significantly higher in patients with hepatic steatosis (15,16). However, levels of serum GGT have been shown to correlate with hepatic triglyceride contents (17). Recently, Chen et al showed that serum ALT levels independently

correlated with the hepatic triglyceride contents in a study of 475 obese subjects. Additionally, they suggested that ALT was more accurate to predict NAFLD instead of AST or GGT. In this study of Chen et al, hepatic fat accumulation was evaluated by magnetic resonance spectroscopy without of liver biopsy (18). Among our patients with and without of steatosis, there were no statistically significant difference between the levels of AST, ALT and GGT. However, levels of liver enzymes were higher in the group with steatosis except AST. But, this increase did not achieve statistical significance probably due to the small number of patients. Similar to our study, Peppercorn et al. found no relationship between liver enzyme levels and presence of hepatosteatosis in patients with advanced hepatic steatosis after receiving 5-FU and folinic acid (8). However, we must take into consideration that the number of patients in our study and in the study of Peppercorn et al were low (8). So, to make a definitive conclusion may not be correct.

Bower et al studied 208 patients with colorectal cancer who experienced hepatic resection due to liver metastases. In their study, they showed that body mass index(BMI) was related with chemotherapy associated liver damage (19). Also, Brouquet et al in their evaluation of 146 patients with colorectal cancer found that high BMI was related with chemotherapy associated liver damage (20). In our study, in a similar way with Bower and Brouquet et al, BMI was significantly higher in the patients with hepatosteatosis. Therefore, risk of chemotherapy associated liver damage is higher in patients with higher BMI, and we must be more careful about hepatotoxic medications / treatments in patients with high BMI. In our study, hepatosteatosis was found 54.5% in patients receiving chemotherapy due to hematological malignancies beside having persistent liver enzyme elevation. In these patients, there was no additional risk factors that could lead to hepatic steatosis. So, The steatosis was thought to be associated with chemotherapy in these cases. In comparison of the groups with and without hepatosteatosis, the only statistically significant difference was observed for BMI. The reason for this may be the small number of patients in our study. In our study, hepatic steatosis was diagnosed by liver biopsy. We believe that it would be appropriate to perform liver biopsy in order to determine the etiology in patients with persistently high liver enzymes after chemotherapy. In addition to this, NAFLD has risk of progression to fibrosis and cirrhosis in patients cured with chemotherapy. So, long term follow-up should be done carefully.

In conclusion, in our study incidence of chemotherapy associated hepatic steatosis was found high in the patients receiving treatment for hematologic malignancies. Studies in the literature are only about patients with colorectal malignancy. Larger studies are needed to investigate the risk factors for chemotherapy associated hepatosteatosis in different malignancy groups.

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