Development of Hepatic Steatosis After Chemotherapy for Non-Hodgkin Lymphoma

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Nonalcoholic fatty liver disease is the most common liver disorder in the developed world. Although typically reflecting caloric overload, it can also be secondary to drug toxicity. We aimed to describe the incidence and risk factors for *de novo* steatosis during chemotherapy for non-Hodgkin lymphoma (NHL). In this retrospective case-control study, adult patients with NHL were treated with rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine (R-CHOP) or R-CHOP + etoposide (EPOCH-R). Patients with liver disease or steatosis were excluded. Abdominal computed tomography was performed pretreatment and at 3- to 6-month intervals and reviewed for steatosis. Patients with *de novo* steatosis were matched 1:1 to controls by age, sex, and ethnicity. Of 251 treated patients (median follow-up 53 months), 25 (10%) developed *de novo* steatosis, with the vast majority (23 of 25; 92%) developing it after chemotherapy. Of those, 14 (61%) developed steatosis within the first 18 months posttreatment and 20 (87%) within 36 months. Cases had higher baseline body mass index (BMI; mean ± SD, 29.0 ± 6.5 versus 26.0 ± 5.2 kg/m^2; $P = 0.014$) and hyperlipidemia (12% versus 2%; $P = 0.035$). Although their weights did not change during chemotherapy, BMI in cases increased by 2.4 ± 2 kg/m^2 (mean ± SD) from end of treatment to steatosis compared to 0.68 ± 1.4 in controls ($P = 0.003$). Etoposide-containing regimens were associated with a shorter time to steatosis (median 34 weeks versus 154 weeks; $P < 0.001$) despite similar baseline risk factors. *Conclusion:* The recovery period from NHL chemotherapy appears to be a "hot spot" for development of fatty liver, driven by early posttreatment weight gain, especially in subjects with baseline risk factors. (*Hepatology Communications* 2019;3:220-226).

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver enzyme abnormalities in the developed world[(1)] and a major cause for liver transplantation.[(2)] Patients with NAFLD are at risk for metabolic comorbidities, such as cardiovascular disease, cerebrovascular events, and diabetes.[(3,4)] Moreover, patients with steatohepatitis are at risk for liver-related morbidity and mortality.[(5,6)] In most patients with NAFLD, hepatocyte fat accumulation reflects caloric excess and is associated with obesity and the metabolic syndrome. However, fatty liver can also be a feature of drug-induced liver injury (DILI) and was described in patients treated with methotrexate, amiodarone, antiretrovirals, and estrogen receptor modulators, such as tamoxifen.[(7)] Fatty liver development was also reported as a consequence of cancer

chemotherapy, especially for colorectal cancer[8,9] with treatments containing 5-fluorouracil or irinotecan.[10] However, due to heterogeneity in treatment regimens, the true incidence and prevalence of chemotherapy-associated fatty liver is difficult to ascertain.

In this study, we assessed the incidence and timeline of chemotherapy-associated fatty liver using non-Hodgkin lymphoma (NHL) as a model. NHL was selected because it does not typically metastasize to the liver like solid malignancies and has a relatively standardized treatment. Furthermore, all subjects with NHL undergo cross-sectional imaging (including the liver) at regular intervals as part of treatment evaluation, allowing for minimization of selection bias. Our goal was to identify the incidence of *de novo* steatosis occurring during treatment of NHL, its risk factors, and its impact on treatment outcomes.

Patients and Methods

STUDY POPULATION AND TREATMENT

We carried out a retrospective, chart-based, case-control study of adult (>18 years) patients who were enrolled in one of two clinical trials for treatment of NHL (clinicaltrials.gov NCT00001337 and NCT00234351) at the National Institutes of Health Clinical Center.

Patients were enrolled between 1993 and 2012 and received at least one dose of a planned cancer chemotherapy medication, either rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine (R-CHOP) or dose-adjusted R-CHOP + etoposide (EPOCH-R)

regimen for six 3-week cycles. Enrollment criteria to the treatment trials included presence of NHL, no prior chemotherapy treatment, no serious concomitant medical issues, and no human immunodeficiency virus infection. Computed tomography (CT) was performed at baseline and at 3- to 6-month intervals.

We excluded from the analysis patients with viral hepatitis, stem cell transplantation, use of systemic methotrexate, or known anatomic involvement of the liver with lymphoma. Because the study focused on incident fatty liver developing on treatment, we also excluded subjects with steatosis on baseline imaging.

All patients provided written informed consent to participate in the original treatment trials. This retrospective analysis was approved by the Diabetes and Digestive and Kidney Diseases/National Institute of Arthritis and Musculoskeletal and Skin Diseases Institutional Review Board.

RADIOLOGIC ASSESSMENT

Electronic medical records of the study patients were screened for CT results containing the phrases "fatty liver," "steatosis," "liver fat," or "fat accumulation." If any of the phrases was detected, all CT scans for that patient were reviewed blindly by a single radiologist and assessed for presence and severity of steatosis. Steatosis was defined as liver density <50 Hounsfield units (HUs) on noncontrast CT or liver–spleen difference <40 HUs on a contrast scan.[11,12] The presence of focal fatty infiltration was not sufficient by itself to define steatosis. Muscle mass was assessed from CT using the psoas muscle index (PMI), calculated by the area of the psoas muscles at the level of L3 divided by the height squared.[13]

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ASSESSMENT OF LIVER DISEASE

Medical and research records of all cases and controls were reviewed. Data extracted included details of NHL diagnosis and treatment, other medical conditions, anthropometric measurements, liver-related blood tests, need for hepatology consult or liver biopsies, and clinical outcomes. Noninvasive markers of fibrosis, including the aspartate aminotransferase (AST)-to-platelet ratio index (APRI),[14] AST/alanine aminotransferase (ALT) ratio, and NAFLD fibrosis score (NFS),[15] were calculated.

DATA ANALYSIS AND STATISTICAL METHODS

Patients with *de novo* steatosis (i.e., appearance of fatty liver after their initial scan) were defined as cases. Controls were selected from the same patient population and matched to cases 1:1 by age (±5 years), sex, and race/ethnicity. All CT scans for controls were reviewed to ensure the absence of steatosis. Cases were compared to the rest of the study cohort (unpaired analysis) and to matched controls (paired analysis). Baseline parameters were obtained from assessments immediately prior to chemotherapy initiation (typically within 7 days). Mann-Whitney U and Wilcoxon signed rank tests were used for significance testing in unpaired and paired analyses, respectively. Statistical analyses were performed using GraphPad Prism version 7a and SPSS version 20.

Results

We assessed 267 patients with NHL who were followed up for a median of 53 months (range, 2.8-65 months). Sixteen patients were excluded from the study: 11 due to age <18 years, 6 due to methotrexate treatment, 6 due to chronic viral hepatitis, and 2 due to steatosis on baseline imaging (some patients had more than one cause for exclusion). The final study cohort included 251 patients (Supporting Fig. S1).

The baseline prechemotherapy characteristics of the study cohort are shown in Table 1. *De novo* steatosis developed after a median of 62 weeks in 25 (10%) patients (Fig. 1A). Of these, only 2 (8%) developed steatosis during chemotherapy and 23 (92%) developed it after treatment. Of the 23, 14 (61%) developed steatosis during the first 18 months posttreatment and 20 (87%) during the first 3 years (Fig. 1B).

TABLE 1. BASELINE (PRETREATMENT) CHARACTERISTICS

Criteria	Entire Cohort	Steatosis	No Steatosis	P Value
N	251	25	226	
Age (years)	47 (18)	49 (10)	47 (18)	0.34
BMI (kg/m^2)	26.3 (5.4)	29 (6.5)	26 (5.2)	0.014
Male	135 (54%)	17 (68%)	118 (52%)	0.13
Race				0.22
White	193 (77%)	22 (88%)	171 (76%)	
Asian	12 (5%)	1 (4%)	11 (5%)	
Black	31 (12%)	1 (4%)	30 (13%)	
Other	15 (6%)	1(4%)	14 (6%)	
ALT (U/L)	36 (52)	33 (23)	36 (55)	0.18
Glucose (mg/dL)	106 (31)	113 (30)	106 (31)	0.04

Data collected before chemotherapy initiation and presented as mean (SD) or number (%). *P* values for comparisons between patients who subsequently developed steatosis and those who did not, using Mann-Whitney test for continuous variables and chi-square test for categorical variables.

BASELINE PREDICTORS OF STEATOSIS DEVELOPMENT

At baseline, cases had higher body mass index (BMI) compared to the rest of the study cohort (mean ± SD, 29.0 ± 6.5 versus 26.0 ± 5.2 kg/m^2; $P = 0.014$) and slightly higher blood glucose levels but did not differ in other parameters, such as age, sex, ethnicity, or liver enzymes (Table 1). Cases were more likely to have dyslipidemia (12% versus 2% in the rest of the cohort; $P = 0.035$), but no difference was seen in rates of diabetes (4% in cases versus 3.3% in the cohort; $P = 0.8$) or hypertension (12% versus 8%; $P = 0.5$). On multivariate Cox regression, BMI ($P = 0.001$) and dyslipidemia ($P = 0.034$) were significantly associated with developing steatosis, whereas blood glucose levels did not retain significance ($P = 0.29$). For a more accurate analysis, we compared cases to nonsteatotic controls matched for age, sex, and race. Similar to the comparison with the entire cohort, cases had a higher BMI (Fig. 2A) and blood glucose level (mean ± SD, 113 ± 30 mg/dL versus 96 ± 17 mg/dL; $P = 0.038$) compared to matched controls and were more likely to have dyslipidemia (12% versus 0%). Muscle mass, assessed by PMI, did not differ between groups (mean ± SD, 8.7 ± 1.8 cm^2/m^2 versus 8.6 ± 2.3 cm^2/m^2; $P = 0.98$). Thus, it appears that subjects with metabolic risk factors at baseline are more likely to develop steatosis after lymphoma treatment.
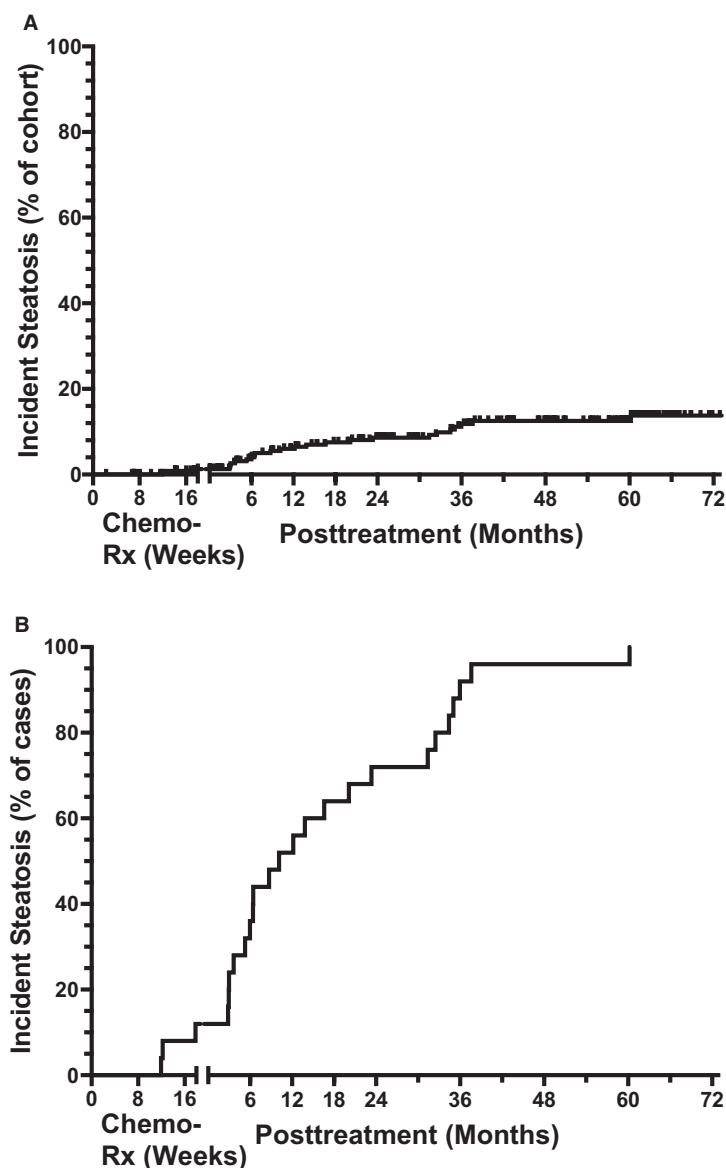
FIG. 1. Incidence of *de novo* steatosis during and after treatment for lymphoma. (A) Cumulative incidence among all subjects. (B) The majority of subjects with *de novo* steatosis present during the first 18 months following chemotherapy. Abbreviation: ChemoRx, chemotherapy.

WEIGHT CHANGE AND STEATOSIS DEVELOPMENT

Eighteen weeks of chemotherapy were not associated with weight change in either cases or matched controls (BMI change, mean ± SD, –0.12 ± 1.5 kg/m^2 versus –0.35 ± 2 kg/m^2; Fig. 2B). In contrast, from the end of chemotherapy to the first occurrence of steatosis, BMI increased by 2.4 ± 2 kg/m^2 (mean ± SD) in cases compared to 0.7 ± 1.4 kg/m^2 in matched

controls over the same time period (P = 0.003; Fig. 2C) as did muscle mass (mean ± SD, 0.8 ± 0.9 cm^2/m^2 in cases versus 0.06 ± 1.1 cm^2/m^2 in controls; P = 0.02).

IMPACT OF TREATMENT REGIMEN

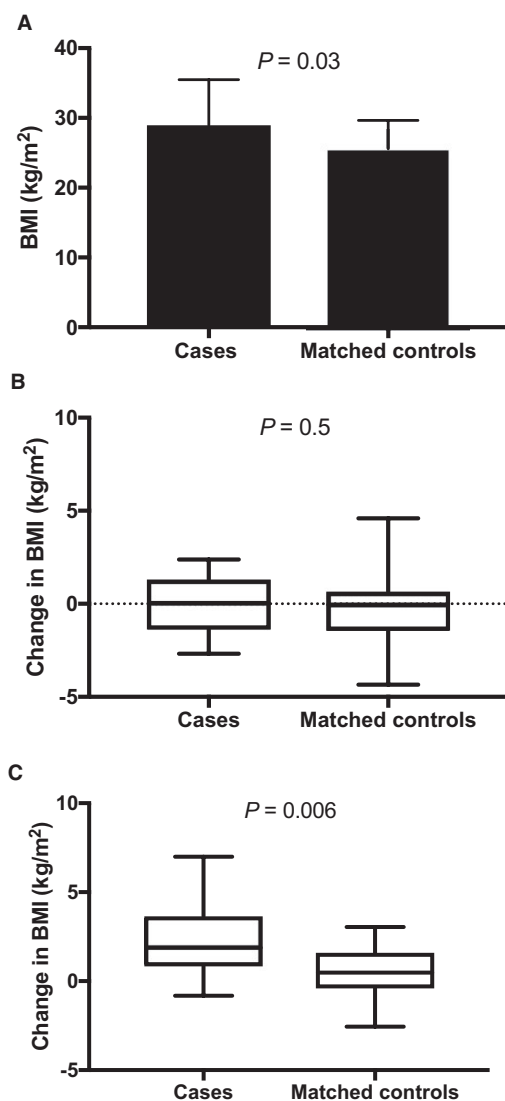EPOCH-R was used in 117 (47%) patients and R-CHOP in 134 (53%); baseline characteristics

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FIG. 2. BMI impact on *de novo* steatosis in cases and age-, ethnicity-, and sex-matched controls (n = 25). (A) Baseline BMI (data represent mean ± SD). (B) Change in BMI from treatment initiation to end of cancer chemotherapy. Data are shown as median (mid horizontal line), IQR (closed box), range (whiskers). (C) Change in BMI from end of chemotherapy to first occurrence of steatosis (median, IQR, range). *P* values from paired Wilcoxon signed rank test. Abbreviation: IQR, interquartile range.

did not differ between the two regimens. The overall rate of *de novo* steatosis was similar, occurring in 12 (10.3%) of the patients treated with EPOCH-R and in 13 (9.7%) of the R-CHOP group (*P* = 0.84). However, steatosis occurred earlier in the EPOCH-R group after a median of 34 weeks (95% confidence interval [CI], 17-51 weeks) compared to 154 weeks

(73-235 weeks) in the R-CHOP group (*P* < 0.001), despite a lower posttreatment rise in BMI in the EPOCH-R group (mean ± SD, 1.6 ± 1.4 kg/m^2 versus 3.7 ± 2.6 kg/m^2; *P* = 0.03) (Supporting Fig. S2).

IMPACT OF STEATOSIS ON CLINICAL OUTCOMES

There was no difference in lymphoma remission rates between cases and matched controls. There were no instances of chemotherapy dose reductions or delays due to liver toxicity, and no hepatology consults were requested.

ALT at the time of steatosis did not differ between cases and matched controls (mean ± SD, 37 ± 16 U/L versus 34 ± 20 U/L; *P* = 0.4). Surrogate markers of fibrosis did not differ between cases and matched controls at the time of steatosis, including APRI (mean ± SD, 0.38 ± 0.24 versus 0.37 ± 0.19; *P* = 56), AST/ALT ratio (mean ± SD, 0.74 ± 0.26 versus 0.83 ± 0.29; *P* = 0.16), and NFS (mean ± SD, –1.7 ± 1.26 versus –2.1 ± 1.0; *P* = 0.25), and no subject had NFS suggestive of advanced fibrosis (>0.676). However, this should be interpreted with caution because these scores were not validated in subjects with hematologic disorders.

Discussion

In this study, we evaluated the rate of *de novo* hepatic steatosis in patients treated for NHL with R-CHOP or EPOCH-R regimen. Only 1% of subjects developed steatosis during the actual 4 months of cancer chemotherapy, suggesting the regimens do not have a direct hepatotoxic effect. In contrast, 8% of subjects developed *de novo* steatosis within the first few years after treatment, suggesting a causal association. Steatosis was more likely to develop in subjects with baseline metabolic risk factors, such as obesity and dyslipidemia, but the major risk factor appears to be weight gain in the early posttreatment period.

The liver plays an important role in drug metabolism and is predisposed to injury from medications and toxic intermediate metabolites. Cancer chemotherapy has been associated with liver injury with a spectrum that ranges from asymptomatic transaminase elevation to severe liver dysfunction and death.[16] DILI can take many forms, one of which is

the development of drug-induced steatosis or steatohepatitis.[17] This can also be seen with various cancer chemotherapies, a disorder termed "chemotherapy-associated steatohepatitis (CASH)" with a variable latency from exposure, depending on the specific agent and mechanism of injury.[17] The frequency of CASH is unknown and likely underestimated because of lack of awareness. When radiologic studies are specifically interrogated for the presence of steatosis, CASH is not uncommon; for example, a retrospective review of liver imaging found that oral 5-fluorouracil treatment induced steatosis in 35% of subjects.[18] Whether CASH influences treatment outcomes and survival rates is unclear.[19,20]

We focused on patients with NHL for several reasons. All the components of R-CHOP and EPOCH-R have been associated with hepatotoxicity,[16] but CASH has not been described; however, to the best of our knowledge, this has not been formally studied. NHL treatment also offers a unique opportunity because patients have routine and frequent cross-sectional imaging of the liver, despite the absence of direct liver involvement in the disease, minimizing bias.

The occurrence of *de novo* steatosis during chemotherapy was at a negligible rate. This cannot be attributed to "protection" by chemotherapy-induced weight loss, as weight change was minimal, reflecting current standards of supportive care. Thus, we conclude that chemotherapy-associated steatosis and CASH are not a major concern for patients treated with R-CHOP or EPOCH-R.

In contrast, we identified a marked risk of *de novo* steatosis within the first few years after treatment, predominantly within the first 18 months. Risk factors were higher BMI and dyslipidemia at baseline and weight gain posttreatment. We did not identify sarcopenia as a cause for steatosis. Importantly, steatosis was not associated with clinical outcomes, and surrogate markers do not suggest progression to advanced liver disease at the time of steatosis development. However, these surrogates (APRI, AST/ALT, and NFS) may not be valid in subjects with hematologic disorders, and advanced liver injury is likely to require a longer duration to develop.

There could be several potential explanations for our findings. First, it is possible that our findings are unrelated to NHL treatment and reflect the natural incidence of NAFLD in the population. However, if this were the case, we would expect steatosis to occur at a stable rate throughout the study period. The accelerated rate in the early period and later plateau argue against this explanation.

Second, it is possible that patients had NAFLD prior to developing NHL, but weight loss due to their disease led to loss of liver fat by the time they presented for treatment; in that context, the posttreatment *de novo* steatosis could be characterized as recurrence of baseline NAFLD after recovery and unrelated to treatment. We do not have records of weights prior to developing lymphoma, but the fact that patients who developed steatosis were still heavier at baseline argues against this explanation.

Third, the increase in steatosis could be purely a reflection of posttreatment weight gain. An increase in body weight and obesity was described in survivors of breast cancer[21] and childhood leukemia.[22] Lynce et al.[23] identified increased risk of posttreatment weight gain in adult lymphoma survivors to be a risk factor for subsequent weight gain. Our results show that this weight gain is already associated with a direct hepatic consequence.

Finally, it is possible that, in predisposed subjects with elevated BMI and dyslipidemia, cytotoxic treatment and weight gain serve as a combined second hit and induce a cascade of events that leads to an even higher risk of liver fat accumulation. A direct role for the cytotoxic agents is supported by our unexpected finding of a difference between regimens, where EPOCH-R was associated with a shorter time to development of steatosis. Etoposide is a semisynthetic agent that binds to and inhibits topoisomerase II, preventing repair of DNA breaks. To date there are no reports of etoposide-induced steatosis, although it does impact cholesterol metabolism through its effects on hepatic cholesteryl ester transfer protein.[24] EPOCH-R also differs from R-CHOP in the delivery of doxorubicin (infusional versus bolus), which may impact hepatic toxicity, and in a higher prednisone dose, although this is unlikely to result in a delayed effect.

The strengths of our study are the relatively high number of patients, the standardization of treatment and imaging procedures as the subjects were enrolled in clinical trials, the long duration of follow-up, and the careful review of the imaging by a single expert radiologist to determine the presence of fatty liver. A main limitation of our study is its retrospective

chart-based design with its inherent limitations, essentially limiting the analysis to data that had already been collected. Importantly, several metabolic characteristics, such as insulin, dietary habits, or exercise, are missing. Another limitation is the reliance on CT scans to diagnose steatosis, as these were the only imaging studies available. Although CT is not ideal for quantifying liver fat, it is highly specific in detecting moderate to severe steatosis.[12] Thus, we may be underestimating the total number of subjects with steatosis, limiting our ability to assess multiple predictors and draw robust conclusions. We were also unable to assess whether steatosis was accompanied with steatohepatitis and significant liver damage. Finally, findings in NHL may not be generalizable to other cancer treatments.

In conclusion, our study demonstrates that post-treatment weight gain is clearly associated with an impact on the liver in patients with NHL. With the current favorable outcome of treatments for NHL, caregivers and patients should be aware of the need to maintain metabolic health and avoid weight gain, especially within the early postchemotherapy period.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1304/suppinfo.