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A case of blood triglyceride increased induced by ABVD therapy for classical Hodgkin lymphoma

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ABSTRACT

There are no reports of blood triglyceride (TG) levels increasing with the ABVD regimen. Herein, we present a case of Hodgkin's lymphoma that exhibited ABVD-induced blood TG increase. The patient was a 40-year-old Japanese man. Empiric therapy was initiated using the ABVD regimen for Hodgkin lymphoma. On day 58, the fasting blood TG concentration increased to 1,451 mg/dL. Since no adverse events were noted, 0.2 mg/day of pemafibrate was administered, and the ABVD regimen was continued. Blood TG levels should be periodically monitored during ABVD administration for the patients who are at high risk of increased blood TG levels.

1. Introduction

The ABVD regimen with doxorubicin (DXR), bleomycin (BLM), vinblastine (VBL), and dacarbazine (DTIC) as combination therapy is used as the first-line treatment for classical Hodgkin lymphoma [1]. The most common adverse events associated with ABVD regimen are neutropenia, nausea/vomiting, and alopecia [2]. Additionally, long-term complications associated with ABVD regimen include cardiopulmonary toxicity [3]. Increased blood triglyceride (TG) levels are generally caused by diet and rarely by medication. Among anticancer drugs, capecitabine has been reported to increase fasting blood TG levels [4,5]. In the current report, we present the case of a patient with Hodgkin lymphoma who experienced ABVD-induced blood TG increased.

2. Case

The patient was a 40-year-old Japanese man (height: 172.5 cm; weight: 72.6 kg). The patient's smoking history indicated that he smoked two packs of cigarettes per day (Brinkman index, 800). The patient also reported that he drank alcohol twice a week and consumed outside food twice daily.

On day −40, the fasting serum triglyceride (295 mg/dL) and low-density lipoprotein cholesterol (LDL-Cho; 219 mg/dL) levels were higher than normal at baseline (Fig. 1). The patient was referred to our clinic with the primary complaint of a mass in the right axilla. Positron emission tomography-computed tomography (PET-CT) showed abnormal accumulation in the enlarged lymph nodes from the right supraclavicular fossa to the axillary region. There was no accumulation in other tissues. An axillary lymph node biopsy revealed a diagnosis of mixed-cellularity classical Hodgkin lymphoma, CS IIA, and PS 0. The patient was in the good prognosis group based on the German Hodgkin Study Group, European Organization for the Research and Treatment of Cancer, and National Comprehensive Cancer Network 2009, and in the poor prognosis group based on the National Cancer Institute of Canada/Eastern Cooperative Oncology Group (age and mixed-cellularity were applicable).

Fig. 1 depicts the clinical course of the patient. Day 1 was defined as the first day of the ABVD regimen administration. Empiric therapy was initiated using ABVD (25 mg/m^2 DXR, 10 mg/m^2 BLM, 6 mg/m^2 VBL, and 375 mg/m^2 DTIC IV) on days 1 and 15, with repeated cycles every 28 days for classical Hodgkin lymphoma (Fig. 1. Day 1). A blood test on day 28 revealed that the fasting blood TG concentration had increased to Grade 3 (913 mg/dL). After the second course, complete response (CR) was achieved, based on PET-CT results. Therefore, we continued treatment with the ABVD regimen for six courses. On day 58 (Fig. 1), the fasting blood TG concentration increased to grade 4 (1451 mg/dL). Since there were no adverse events associated with increased blood TG levels, such as pancreatitis (Day 58; Amylase, 57 IU/L) or pseudo-

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hyponatremia (Day 58; sodium, 140 mEq/L), 400 mg/day of bezafibrate was initiated from day 71, and the ABVD regimen was continued. However, his fasting blood TG concentration decreased to grade 3 (700 mg/dL) on Day 114. Therefore, bezafibrate was switched to pemafibrate 0.2 mg/day. The sixth course of ABVD therapy was completed on day 156. After completion of ABVD therapy, the fasting blood TG level improved to grade 1 (day 191, 329 mg/dL). In addition, we confirmed that CR was achieved when the PET-CT results showed no evidence of lymphomatous enlargement or abnormal accumulation. Medical therapy with pemafibrate was continued after the completion of chemotherapy to increase blood TG levels. The patient continued follow-up for classical Hodgkin's lymphoma every three months on an outpatient basis.

3. Discussion

This is the first case report of an ABVD regimen-induced TG increase in a patient with classical Hodgkin lymphoma. Anticancer drugs, such as tamoxifen, protease inhibitors, mTOR inhibitors, some immunosuppressants, interferon, L-asparaginase, bexarotene, and antipsychotic drugs, have been reported to cause dyslipidemia [6]. Additionally, capecitabine and docetaxel have been reported as potential agents that increase blood TG levels [4,5,7]. However, the underlying mechanism remains unclear.

There are few reports on blood TG increased with the ABVD regimen. Our investigation of increased blood TG levels following DXR, BLM, VBL, and DTIC administration in the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) is shown in Table 1. After excluding duplicates from the case IDs, a total of 18 cases were reported as "Blood Triglycerides Increased." Based on the concomitant drug, only one patient was considered to have been administered the ABVD regimen. These results suggest that ABVD-induced blood TG increased may occur, although this has not yet been reported in a published report.

Table 1
"Blood triglycerides increased" observed in case reports of doxorubicin hydrochloride, including ABVD regimen.

	DXR	BLM	VBL	DTIC
All adverse event reports, n	38,366	8111	2814	27
"Blood triglycerides increased" or "Blood triglycerides abnormal" reports, n (%)	17 (0.044)	1 (0.012)	3 (0.106)	0 (-)

DXR: Doxorubicin hydrochloride; BLM: Bleomycin sulfate; VBL: Vinblastine sulfate; DTIC: dacarbazine citrate; FAERS: the U.S. Food and Drug Administration's Adverse Event Reporting System; ABVD regimen: doxorubicin, bleomycin, vinblastine, and dacarbazine combination therapy.

We discuss the cause of the blood TG increased in our case report. The possible causes of the blood TG increased were diet, renal and hepatic diseases, and hemophagocytic syndrome. First, we examined the effects of the diet. Before initiating the ABVD regimen, the patient's fasting blood TG level was 239 mg/dL, which was higher than the reference value (150 mg/dL). Additionally, on the same day, LDL-Cho level was 253 mg/dL and the high-density lipoprotein cholesterol (HDL-Cho) was 28 mg/dL; both were higher than the reference values. Low HDL cholesterol levels may also be due to classical Hodgkin lymphoma. The attending physician confirmed that there was no change in the patient's diet. As there was no increase in LDL-Cho levels during the treatment period, we ruled out the possibility of a diet-induced increase

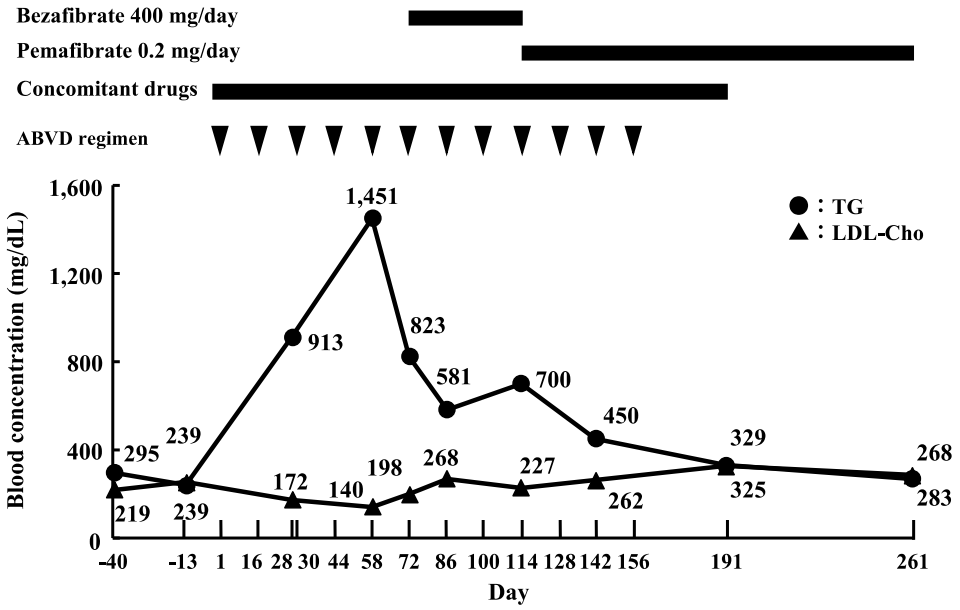

Fig. 1. The clinical course of the present case is presented here. The patient's blood TG concentration and LDL-Cho is presented in the graph. The laboratory data is presented in the table below. Day 1 of the graph indicates the day when the patient was first administered with the ABVD regimen. ABVD regimen: doxorubicin, bleomycin, vinblastine, and dacarbazine combination therapy. Concomitant drugs were trimethoprim-sulfamethoxazole combination, fluconazole, esomeprazole, and febuxostat. TG: triglyceride; T-Bil: Total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γ-GTP: gamma-glutamyl transpeptidase; LDL-Cho: low-density lipoprotein cholesterol; HDL-Cho: High-density lipoprotein cholesterol; AMY: Amylase; Na: Sodium.

	Day -13	Day 28	Day 58
T-Bil (mg/dL)	0.4	0.3	0.3
AST (IU/L)	31	43	34
ALT (IU/L)	57	71	64
ALP (IU/L)	89	84	76
γ-GTP (IU/L)	58	167	161
HDL-Cho (mg/dL)	28	32	29
AMY (IU/L)	51	63	62
Na (mEq/L)	141	140	140

in blood TG levels. Next, the possibility of other diseases was considered. As the patient's renal function on day 28 was normal (serum creatinine, 0.67 mg/dL; creatinine clearance, 148 ml/min; albumin, 4.1 g/dL), nephrotic syndrome was also ruled out. Blood tests did not reveal any abnormalities in liver function. Finally, PET-CT results indicated CR; therefore, classical Hodgkin lymphoma was suggested to improve. Furthermore, there was no fever, splenomegaly, or cytopenia in the peripheral blood (hemoglobin 16.6 g/dL, platelets 26.3×10^4 /μL), no hemophagocytosis in the periphery, or no bone marrow examination. There was elevated ferritin (205.1 μg/L) and soluble interleukin-2 receptor (1762 U/mL). Therefore, hemophagocytic syndrome was excluded. Therefore, evaluation was performed using the Naranjo scale, and a score of 5, which is classified as "probable," was obtained [8]. The drugs used concomitantly before and after the occurrence of hypertriglyceridemia were bezafibrate, pemafibrate, a trimethoprim-sulfamethoxazole combination, fluconazole, esomeprazole, and febuxostat. The Naranjo Score for concomitant medications was evaluated, with bezafibrate and pemafibrate scoring 3 and other drugs scoring 5. The Naranjo score for the ABVD regimen was five points. However, there have been no reports of blood TG increase with each of the concomitant medications used alone or due to concomitant chemotherapy drugs by hematologists. In contrast, an increase in blood TG levels has been reported for regimens containing anthracycline [9]. Progressively increasing blood TG levels were observed after initiation of the ABVD regimen. Therefore, we could conclude that the increased blood TG level was most likely due to the ABVD regimen.

This case report has two limitations. First, in this case, the drug that caused the increase in blood triglyceride levels in the ABVD regimen could not be determined. Of the 21 adverse event reports, including "Blood Triglycerides Increased" and "Blood Triglycerides Abnormal," 17 were due to DXR hydrochloride. He et al. reported a significant increase in the blood TG concentration after administering anthracycline.[15] Therefore, we considered DXR to be the most likely causative drug. However, the ABVD regimen is a combination of four anticancer drugs. The possibility of a drug-drug interaction that comprises the ABVD regimen cannot be ruled out. The causative drug is a specific anticancer drug containing DXR. Second, the mechanism by which ABVD increases blood TG levels is unclear. Assuming that DXR is the causative drug, we discuss the possible mechanism underlying the increase in blood TG levels. He et al. [9]. speculated that chemotherapy itself could directly cause endothelial dysfunction and insulin resistance, leading to cytokine alterations resulting in elevated serum lipid levels. In addition, the mechanism of the increase in blood TG levels in hemophagocytic syndrome is thought to be caused by the suppression of lipoprotein lipase activity by tumor necrosis factor (TNF)-alpha. Additionally, plasma TNF-α has been reported to be elevated in patients treated with DXR [10]. Therefore, we hypothesize that the increase in blood TG caused by the ABVD regimen in our case is due to the suppression of lipoprotein lipase activity mediated by DXR-induced elevation of TNF-α. However, it was not possible to clarify the mechanism of the increase in blood TG levels in our case.

4. Conclusion

This case report suggests that the ABVD regimen itself may be a rare potential cause of severe triglyceride elevation. Blood TG increase is a risk factor associated with acute pancreatitis and pseudo-hyponatremia. Therefore, monitoring blood TG levels periodically during the administration of the ABVD regimen for the patients who are at high risk of increased blood TG levels include before chemotherapy for example, dyslipidemia, liver dysfunction, obesity is recommended. Additionally, we found that blood TG levels increased during the administration of the ABVD regimen and could be controlled using fibrates, thereby suggesting that the treatment of classical Hodgkin lymphoma can be continued without discontinuation or reduction of the dosage of drugs.

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Informed consent

Written informed consent was obtained from the patient for publication of this case report. Furthermore, this case report was approved by the Ethics Committee of the Showa University Fujigaoka Hospital (F2020C147).

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