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CASE REPORT

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A case of diffuse large B-cell lymphoma with decompensated alcohol-related liver cirrhosis treated successfully by chemoimmunotherapy

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Key Clinical Message

This report describes a case of diffuse large B-cell lymphoma with MYD88 L265P and KM2DT mutation and decompensated alcohol-related liver cirrhosis. And the treatment is successful in this patient, who had multiple complications and poor prognostic factors.

Abstract

This report describes a case of diffuse large B-cell lymphoma with MYD88 L265P and KM2DT mutation and decompensated alcohol-related liver cirrhosis. The lymphoma showed a complete response with no MYD88 L265P mutation after four courses of combination chemotherapy. Lymphoma is one of the most common malignant tumors, but cases of DLBCL with cirrhosis are much rarer especially with alcohol-related cirrhosis. And we reviewed the relevant mechanisms. Although we did not find a definite association between the pathogenesis of the patient's alcohol-related cirrhosis and that of diffuse large B-cell lymphoma, the treatment is successful in this patient, who had multiple complications and poor prognostic factors.

KEYWORDS

alcohol-related cirrhosis, diffuse large B-cell lymphoma, mechanism, non-Hodgkin's lymphoma

1 | INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are associated with certain lymphoproliferative diseases. HBV and HCV have been identified in lymphoid tissues and are known to have direct effects on lymphoid cells.[1,2] A statistically significant association between chronic HBV infection and non-Hodgkin's lymphoma (NHL) has also been reported,[3] suggesting a pathophysiological link between hepatitis virus infection and lymphatic neoplasms. However, diffuse large B-cell lymphoma (DLBCL) accompanied by decompensated alcohol-related liver cirrhosis is rare. Furthermore, patients with cirrhosis tend to be excluded from clinical trials, so there is limited information on the prognosis of patients with cirrhosis treated according to the available options. This report describes a patient with decompensated alcohol-related liver cirrhosis who developed DLBCL with

MYD88 L265P and KM2DT mutation that was treated successfully by combination chemotherapy.

2 | CASE HISTORY

The patient was a 45-year-old man who presented with a 5-day history of fever that was accompanied by sore throat, rhinorrhea, and chills but no other complaints. He had a history of alcohol-related cirrhosis, diabetes, and cerebral infarction. He had undergone endoscopic selective varices devascularization surgery for gastrointestinal bleeding on two occasions and had also undergone percutaneous superselective celiac arteriography and splenic artery embolization.

2.1 | Investigation

Routine laboratory tests showed pancytopenia (white blood cells 2.56×10^9/L, neutrophils 1.29×10^9/L, lymphocytes 0.97×10^9/L, hemoglobin 72 g/L, and platelets 23×10^9/L). A direct antiglobulin test was positive for C3d and IgG. Serum immunofixation electrophoresis showed an abnormal M protein precipitation band that was identified to be IgM-kappa, and an antinuclear antibody test was weakly positive at 1:100 and of the nuclear spot type. Examination of bone marrow morphology revealed atypical lymphocytes. Bone marrow biopsy revealed bone marrow hyperplasia that was markedly active (hematopoietic area about 90%), a significantly increased proportion of lymphocytes with a small to medium volume and a scattered distribution, and marked decreases in erythroid and granulocyte cells. Positron emission tomography/computed tomography (PET/CT) showed hypermetabolic enlargement of lymph nodes in the superior and inferior diaphragm, splenomegaly with hypermetabolism, a diffuse increase of metabolism in bone marrow, and bone destruction in the medial portion of the left maxillary sinus with localized hypermetabolic soft tissue shadowing. According to PET-CT, the baseline lymph node involvement of the patient are as follows: multiple hypermetabolic enlarged lymph nodes could be seen in bilateral cervical, bilateral subclavian, bilateral axillary, mediastinal, Waldeyer's Ring, splenic hilum, para-aortic, bilateral iliac blood vessels, and bilateral inguinal regions, with a standard uptake value max (SUVmax) of approximately 2.1–17.5 and short diameter of approximately 5–24 mm. DNA sequencing showed that MyD88 L265P (3p22.2, exon 5), CXCR4 (2q22.1, exon 2, p.V340Rfs*5), and KMT2D (12q13.12, exon 39, p.Q3863_H3864insQ) were positive. Flow cytometry revealed that 38.51% of nuclear cells were abnormal (CD19, CD200, and CD81, kappa expression; FMC7, CD20, partial expression; CD79b, CD25, CD22, sIgM, sIgD, weak expression). Cervical lymph node biopsy showed lymphoproliferative lesions. The immunohistochemistry staining results were as follows: CD20 (+), CD21 (residual follicular dendritic cells, net +), CD23 (residual follicular dendritic cells, net +), CD5 (−), cyclin D1 (−), c-MYC (about 30% +), MUM1 (+), Bc1-2 (+), and Bc1-6 (about 20% +). The nuclear proliferation rate was assessed by Ki-67 staining to be approximately 70%. These findings were consistent with DLBCL in the "not otherwise specified" (NOS) category.

2.2 | Diagnosis

Given that the origin of the activated B-cells was outside the germinal center, the diagnosis was DLBCL (NOS, non-germinal center type, Ann Arbor stage IV, aaIPI score 3, high risk).

2.3 | Treatment

The patient's liver enzymes showed no significant abnormalities, but serum albumin was low. The blood concentration of chemotherapy drugs may have increased compared to normal conditions, leading to a corresponding increase in adverse reactions. Cyclophosphamide has a significant impact on liver function, and it was recommended to reduce the dosage by more than half. Anthraquinone and vincristine are not affected by proteins and liver function, and hormones had no obvious contraindications. Rituximab was not significantly affected by liver function, but it suppressed immune function and increased the risk of hepatitis. Taking into account the above factors, a reduced dose R-miniCHOP regimen was administered for chemotherapy. The patient was treated with eight courses of R-miniCHOP chemotherapy (rituximab 600 mg IV on Day 0, cyclophosphamide 600 mg IV on Day 1, doxorubicin 30 mg IV on Day 1, vincristine 20 mg IV on Day 1, and prednisolone 50 mg PO on Day 1–5). The changes in laboratory indicators during treatment are shown in Figure 1. PET/CT confirmed a complete metabolic remission after four courses of R-miniCHOP (Figures 2 and 3). After four cycles, bone marrow was negative for MYD88L265P, CXCR4, and KMT2D and for minimal residual disease. After eight cycles, PET/CT still showed a complete metabolic response.

3 | DISCUSSION

Large B-cell lymphoma has an incidence of 5–7 cases per 100,000 cases per year in the general population, but cases of DLBCL with cirrhosis are much rarer.[4,5] In previous studies

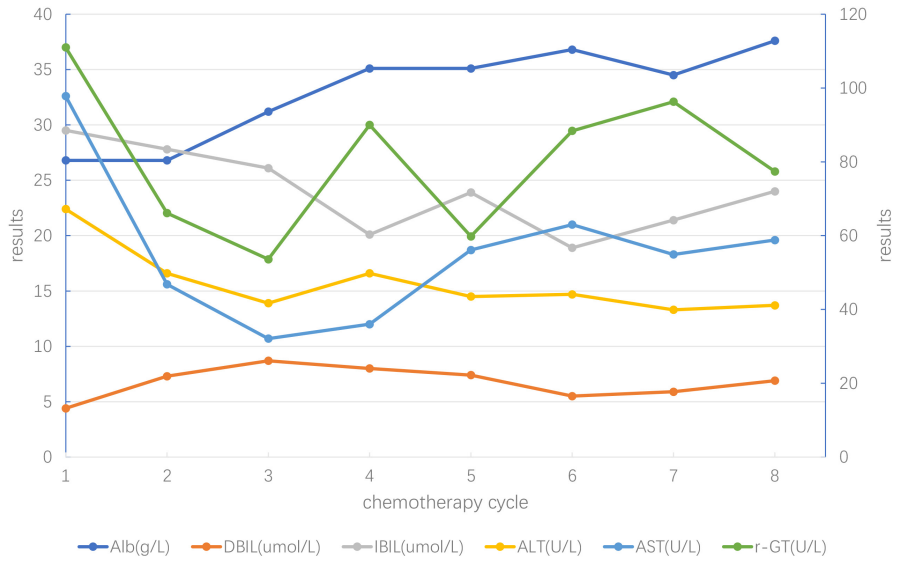

FIGURE 1 Changes in laboratory indicators. The r-GT series is drawn on the secondary axis and the others are drawn on the primary axis. Alb, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, serum direct bilirubin; IBIL, serum indirect bilirubin; r-GT, r-glutamyl transpeptidase.

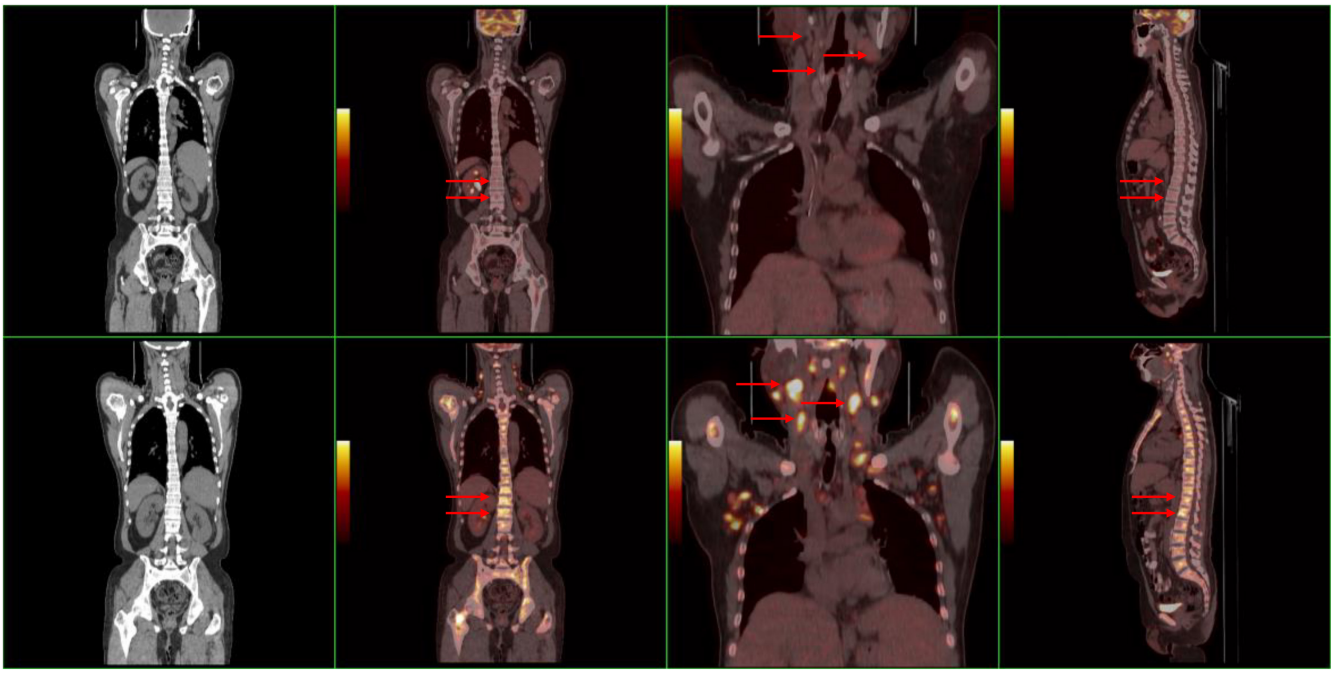

FIGURE 2 Positron emission tomography/computed tomography fusion images. The images obtained before chemotherapy are shown on the second line and those obtained after chemotherapy are shown on the first line. The red arrows indicate hypermetabolism. Before treatment, the patient's bone marrow metabolism was diffusely increased with multiple enlarged hypermetabolic lymph nodes.

of patients with lymphoma and cirrhosis, 62.6% had HCV-related cirrhosis, 13.5% had HBV-related cirrhosis, and 7.8% had alcohol-related liver disease.[6] Moreover, a large retrospective study from a tertiary care center in Mexico found that the most frequent etiology of cirrhosis in patients with lymphoma was HCV (detected in 50% of cases). Ninety percent of these patients had NHL and the most common type was DLBCL with a high International Prognostic Index value.[7] Lymphoma combined with alcohol-related cirrhosis was extremely rare in these studies.

The association between HCV infection and B-cell NHL (B-NHL) has been confirmed in previous studies. A meta-analysis that included 48 studies found that the prevalence of HCV in patients with B-NHL was not only higher than that in the general population but also higher than that in patients with other hematological malignancies, indicating that HCV plays a role in the etiology of B-NHL.[8] A study in a large number of patients with HCV treated with interferon found that the incidence rate of B-NHL was reduced in patients who achieved a sustained virological response.[9] The finding that eradication of the virus can reduce the incidence of B-NHL provided further evidence for the involvement of HCV in the occurrence and development of B-NHL.

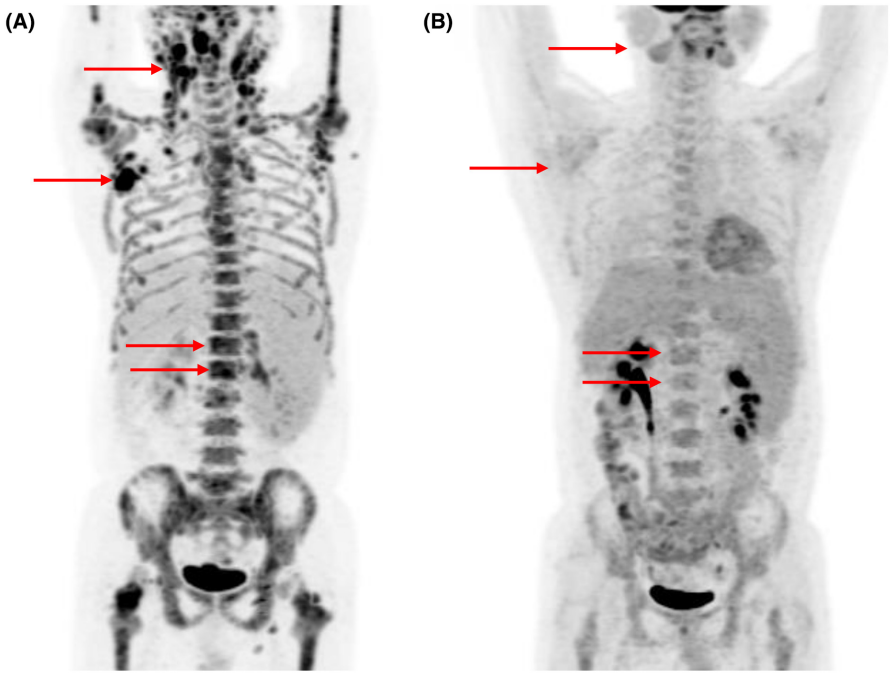

FIGURE 3 Positron emission tomography maximum intensity projection images. (A) Before treatment. (B) After treatment. The red arrows indicate hypermetabolism. Before treatment, the patient had high metabolism in the spine and in cervical and axillary lymph nodes.

HCV can cause various B-cell lymphoproliferative diseases. Chronic HCV infection may result in abnormal proliferation of B-lymphocytes that produce immunoglobulins, leading to diseases ranging from asymptomatic polyclonal hypergammaglobulinemia to mixed cryoglobulinemia vasculitis and ultimately to B-NHL.[10] Moreover, chronic HCV infection has multiple extrahepatic manifestations, the most common of which is circulating cryoglobulin.[11] Cryoglobulinemia is the main risk factor for development of B-NHL.[12] Lymphocytes and hepatocytes have the same CD81 transmembrane receptor, which binds to the envelope viral protein (i.e., protein E2) and decreases the threshold for activation and proliferation of B-cells.[13] These effects can induce hypermutations in immunoglobulin genes. High mutation rates may lead to production of HCV antibodies with low affinity and specificity, which help the virus to evade immune surveillance.[14] A complex process follows, in which the disease progresses from asymptomatic cryoglobulinemia to the clinical syndrome of vasculitis, and ultimately to a dominant B-cell malignancy.[15] The correlation between HCV infection and B-NHL varies according to subtype. For example, the correlation of HCV with marginal zone lymphoma, lymphoplasmacytic lymphoma, and DLBCL has been reported to be stronger than with other subtypes of B-NHL.[16,17]

Chronic HBV infection is also associated with an increased risk of NHL. A study in Taiwan found that patients with HBV infection had a significantly increased risk of DLBCL but not of T-cell NHL or follicular lymphoma.[18] Furthermore, a meta-analysis showed that HBV infection was more strongly correlated with B-NHL than with T-cell NHL. Among the B-NHL subtypes, DLBCL and follicular lymphoma were significantly associated with HBV whereas chronic lymphocytic leukemia/small lymphocytic lymphoma and Burkitt lymphoma were not.[19]

Current knowledge regarding the mechanism via which HBV causes NHL is limited in comparison with that regarding the relationship between HCV and NHL.[20] HBV can bind to peripheral blood mononuclear cells (PBMCs) via pre-S1 protein, and B-lymphocytes and monocytes can bind virus particles more effectively than T-cells.[21] Studies in animal models have confirmed that HBV DNA is integrated into PBMCs and hepatocytes in HBV carriers and individuals who are only positive for anti-HBc.[22,23] Transcription of HBV genes in PBMCs promotes replication and transcription of the virus in these cells, which suggests that the lymphatic system is an important repository for HBV.[24,25] The main mechanisms could be chronic proliferation of B-cells caused by antigen stimulation or polyclonal activation as well as direct HBV infection and the carcinogenic effect of integration of HBV DNA in lymphocytes.[20]

Our patient was diagnosed as DLBCL with alcohol-related liver cirrhosis. B-NHL complicated by alcohol-related cirrhosis is rarer than B-NHL complicated with HCV or HBV, and the mechanism is not clear. However, there has been a report suggesting that the mechanism underlying the association of T-cell lymphoma with alcohol-related cirrhosis may involve the transforming growth factor-beta (TGF-β) signaling pathway. TGF-β is the main regulatory factor in chronic liver disease, which ranges from liver injury, inflammation, fibrosis, through to hepatocellular carcinoma. It also has

inhibitory and apoptotic effects in hepatocytes and promotes differentiation of liver cells during embryonic development and physiological regeneration of the liver. However, in the event of chronic liver injury, there is an increase in the TGF-β level increases, which can lead to activation of stellate cells into myofibroblasts and the death of a large number of liver cells, thereby promoting liver fibrosis and subsequent cirrhosis.[26] TGF-β blocks production of interleukin-2, thereby inhibiting interleukin-2-dependent proliferation of T-cells, in particular cytotoxic $CD8^+$ cells. Furthermore, TGF-β inhibits maturation of T-cells. In malignant hematological diseases, resistance to inhibition of TGF-β occurs mainly via downregulation of TGF-β receptor expression levels.[27] Disruption of the TGF-β signaling pathway promotes development of T-cell lymphoma and leukemia as a result of excessive proliferation of $CD8^+$ T-cells.[28]

DNA sequencing showed that our patient was positive for MyD88 L265P and CXCR4. MYD88 L265P mutation has been reported to be one of the reasons for an unfavorable prognosis in patients with DLBC.[29] CXCR4 expression is also associated with a poor prognosis. CXCR4 has been found to inhibit the response induced by rituximab, and the surface expression level of CXCR4 is negatively correlated with sensitivity to rituximab in reactive DLBCL cell lines.[30] However, our patient had an excellent response to R-miniCHOP chemotherapy.

In conclusion, we have encountered a rare case of DLBCL with alcohol-related cirrhosis. Although the pathogenesis is not yet clear, the patient was successfully treated with combination chemotherapy.

AUTHOR CONTRIBUTIONS

Yan Li: Writing – review and editing. **Ling-zhijie Kong:** Writing – original draft.

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Not applicable.

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No funding was received.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current research are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This case report is submitted for publication with the approval of the Ethics Committee of Hebei General Hospital.

CONSENT

This report was published with the written consent of the patient's relatives.

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