

Long-Term Complete Remission of a Patient With Double-Hit Diffuse Large B-Cell Lymphoma Treated by Chemoimmunotherapy and Chinese Herbal Medicine

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Abstract

Double-hit diffuse large B-cell lymphoma (DHL) is an uncommon subtype of lymphoma which poorly responds to current drug therapies and has low rates of long-term survival in the patients. Herein, we report a case of a 73-year-old Caucasian male who was diagnosed with DHL with double-hit mutations of rearrangement of both c-MYC and BCL2 in November 2013. He commenced the standard R-CHOP-14 chemotherapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone) but changed to dose-adjusted DA-EPOCH-R protocol (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone, and rituximab) in the second and third cycles due to double-hit mutation. Because of intolerance to the intensive therapy, the patient decided to switch to Chinese medicine intervention. From March 2014 to December 2019, he was prescribed with a classical Chinese herbal formula—*Sijunzi Decoction* plus *Prunella vulgaris* based prescriptions. After 2 months of the Chinese herbal medicine intervention, the patient felt his right groin mass disappeared. Imaging follow-up showed no residual masses, and no lymphadenopathy was seen. During the period of Chinese herbal medicine treatment, his adherence and tolerability were well maintained with no adverse events. Imaging surveillances afterward found no evidence of lymphoma recurrence. His regular blood tests indicated that the patient's blood counts were normal and stable; no hematologic toxicity, hepatotoxicity, or nephrotoxicity associated with Chinese herbal medicine were found. Follow-up visits until 2020 found that he had been living and enjoying a good quality of life for over 8 years post-diagnosis. This case study illustrates the potential values of Chinese herbal medicine in DHL treatment, alongside chemo-immunotherapy, and in maintaining long-term survival and satisfactory quality of life for DHL patients. The case report provides clinicians with preliminary evidence of the use of Chinese herbal medicine as a therapeutic strategy in the management of DHL.

Keywords

diffuse large B-cell lymphoma, double-hit lymphoma, complete remission, long term survival, Chinese herbal medicine

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Introduction

Lymphoma is a group of lymphocytic malignancies which is one of the most common hematologic cancers worldwide.¹ Traditionally, lymphoma classifies into Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL); the latter makes up over 85%.² Double-hit diffuse large B-cell lymphoma, also known as double-hit lymphoma (DHL) occurs in around 5.8% of diffuse large B-cell lymphoma (DLBCL), belonging to NHL.³ DHL is a high-grade lymphoma characterized by rearrangements in 2 genes, MYC and BCL2 or BCL6. When an anti-apoptotic gene (BCL2 or

BCL6) and proliferative gene (MYC) present concurrently, this type of lymphoma becomes more aggressive and poorly

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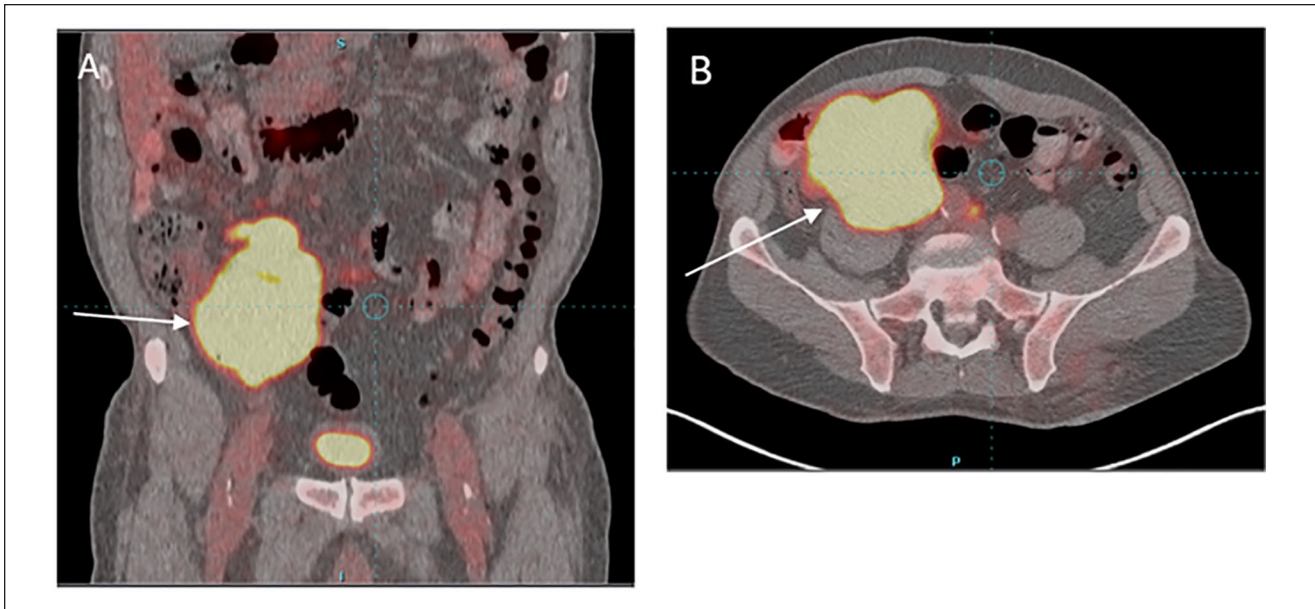


Figure 1. November 2013: There was a large avid portocaval nodal mass (7.8 cm × 8.6 cm) as well as a large mesenteric mass in the right abdomen (A and B).

responds to the current drug therapies. Intensive chemotherapy accompanied by immunotherapy is commonly used for DHL treatment. However, these drugs quite often induce severe neutropenia and thrombocytopenia, and even treatment-related deaths.⁴ Chinese medicine has a long history with its unique theories and therapies for the management of malignancies. Integration of orthodox medicine and Chinese medicine is a major feature of cancer prevention and treatment in China. Over the past 50 years of clinical studies in China, the integrated medicines have shown certain clinical effects and advantages in reducing clinical symptoms of cancer patients, stabilizing the disease, improving patients' quality of life, and prolonging survival rate.⁵ Although there are growing interests in the use of complementary medicines in supportive care of cancer patients in Western countries, relevant clinical studies are still insufficient and an integrated therapeutic model is yet to be established.⁶ Herein, we report the first single case that described a superior outcome of long-term complete remission of a 73-year-old Caucasian male with DHL initiated with chemotherapy and immunotherapy followed by a 5-year treatment of Chinese herbal medicine.

Case Report

A 73-year-old Caucasian male found a painless large mass in his right groin with some enlarged nodes in his neck in November 2013. F-fluorodeoxyglucose (FDG) PET/CT scans showed a large avid portocaval nodal mass (7.8 cm × 8.6 cm) and a large mesenteric mass in the right

abdomen. (Figure 1A and B). There were also para-aortic, common iliac, and presacral avid lymph nodes. The right groin mass was biopsied, revealing a diffuse large B-cell lymphoma (Figure 2A-D). The study of fluorescence in situ hybridization (FISH) further identified evidence of the double-hit mutations with rearrangement of both the *c-MYC* and *BCL2*. Therefore, his disease was diagnosed as double-hit diffuse large B-cell lymphoma, or double-hit lymphoma (DHL). He commenced the standard R-CHOP-14 chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), but changed to dose-adjusted DA-EPOCH-R protocol (dose-adjusted etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone, and rituximab) in the second and third cycles due to cytogenetic abnormalities of double-hit mutation.

Because of intolerance to the intensive chemo-immunotherapy, he stopped the chemotherapy at the third cycle about 7 weeks before he was recommended to our clinic in March 2014. It should be noted that this patient came to Chinese medicine treatment 7 weeks after the third cycle of chemo-immunotherapy which is longer than the usual 4 weeks from prior treatment. Given the duration of action from the drugs, Chinese medicine therapy can be considered as a tandem therapy. In the initial consultation, we clearly explained to him that DHL was associated with a poor prognosis, and failure to complete the chemotherapy cycles might result in rapid disease progression. The patient understood his situation but wished and decided to try Chinese herbal medicine (CHM). He felt his right groin mass was smaller and was recovering from chemo-immunotherapy except for tiredness and indigestion.

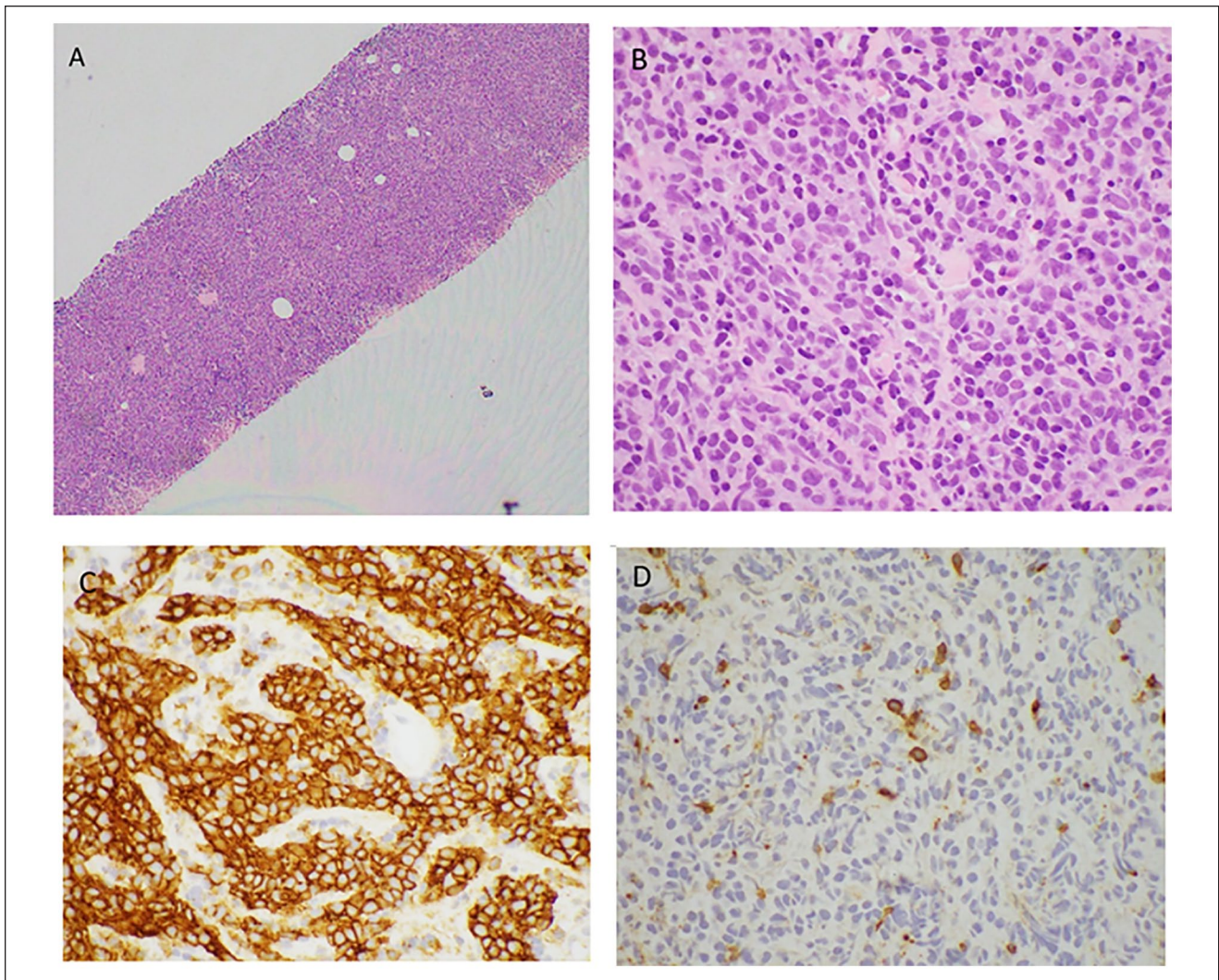


Figure 2. Histomorphology of the right iliac fossa mass. Numerous large, pleomorphic lymphoid cells with abundant mitosis are present (H&E stain, A $\times 100$ and B $\times 400$). The tumor cells were positive for CD20 and CD3 (immunohistochemical stain, C and D $\times 400$), consistent with diffuse large B cell lymphoma.

His hemoglobin was 119 g/L, white cells 3.2×10^9 /L, platelets 106×10^9 /L, lactate dehydrogenase (LDH) 298 U/L, and globulin 15 g/L; otherwise, blood test results were normal. Chinese medicine assessment revealed his tongue color was slightly red with greasy and yellow fur; his pulse was string-like. The major diagnostic pattern of the patient from the perspective of Chinese medicine was heat accumulation, phlegm, and blood stasis, with underlying deficiency of healthy qi. Following the guidelines for Safe CHM Practice of the Chinese Medicine Board of Australia (CMBA), we provided CHM for this patient regularly. These CHMs were ordered from wholesalers in Australia. According to the pattern of Chinese medicine, the basic prescription was *Sijunzi Decoction* plus *Prunella vulgaris* with raw herbs used from March 2014 to March 2017 including *Prunella vulgaris* 20 g, *Sophora flavescens* 12 g, *Scutellaria*

baicalensis 15 g, *Salvia miltiorrhiza* 12 g, *Codonopsis pilosula* 15 g, *Atractylodes macrocephala* 12 g, *Poria cocos* 15 g, and *Glycyrrhiza uralensis* 5 g. The herbs in the prescriptions were amended according to the patient's responses. The CHM was administered daily in 2 separate decoctions: for the first decoction, 1000 ml of cold water was added to the herbal mixture, which was then boiled for approximately 50 minutes to reduce the volume to about 250 ml. This decoction was taken each morning. The remaining herbal mixture was used for making a second decoction which was taken each afternoon. This was prepared by using 750 ml of cold water and boiled for approximately 30 minutes to reduce the volume to about 200 ml.

From April 2017 to December 2019, his CHMs were changed to granule form because the patient preferred to take an easier form of administration. By carefully

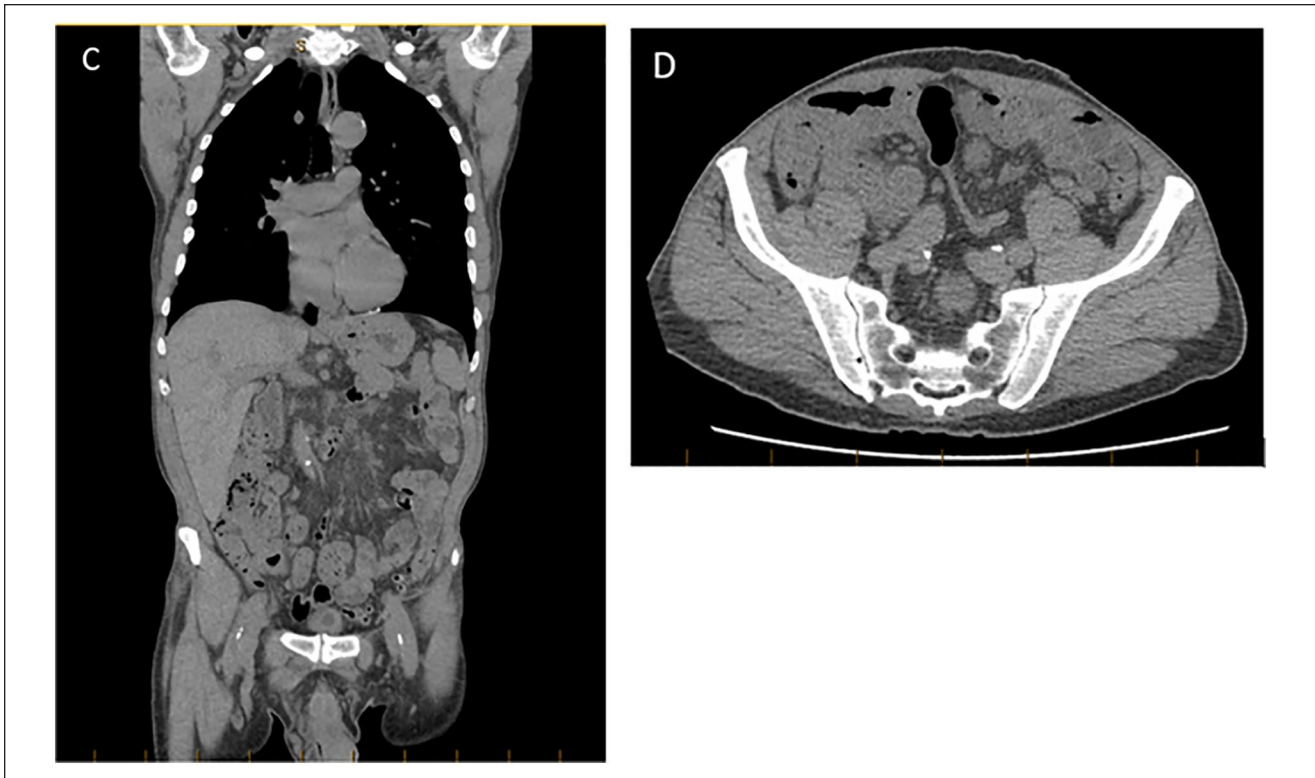


Figure 3. May 2014: the right iliac fossa mass had resolved with no residual mass. No lymphadenopathy was seen (C and D).

considering his condition with completed remission for 3 years, we agreed to shift to an easier form of herbal granules. The basic prescription included *Prunella vulgaris* 3 g, *Sophora flavescens* 2 g, *Hedyotis diffusa* 3 g, *Salvia miltiorrhiza* 2 g, *Astragalus membranaceus* 2 g, and *Ligustrum lucidum* 2 g. The condensed ratio from raw herbs to granules is 5:1. The herbs in the prescription might be amended according to the clinical presentation of the patient. These herbal granules were mixed and taken 2 doses daily. Each dose with 7 g of the mixed granules was dissolved in 200 ml of boiling water and stirred well. One dose was taken in the morning, another in the afternoon.

After 2 months of the CHMs used, the patient felt his right groin mass disappeared. His energy and digestion became normal. Blood tests showed that his hemoglobin and blood platelets became normal. LDH was reduced from 298 to 162 U/L, in the normal range. During the CHMs treatment period from 2014 to 2019, his adherence and tolerability to CHM were well maintained and no adverse events were observed. Follow-up CT imaging on the neck, chest, abdomen, and pelvis in May 2014 showed that the right iliac fossa mass had resolved with no residual mass. No lymphadenopathy was seen (Figure 3C and D). His DHL achieved a complete response to the 1 cycle of R-CHOP-14, 2 cycles of DA-EPOCH-R treatments and CHM. Followed by 5-year CHM management, there was no

evidence of lymphoma recurrence under follow-up CT scan surveillances (Figure 4E and F). His regular blood tests indicated that the patient's blood counts including LDH were reasonably normal and stable; no hematologic toxicity, hepatotoxicity, or nephrotoxicity from CHMs were identified. Further follow-ups until 2020 found that he had been living and enjoying a good quality of life almost 8 years post-diagnosis.

Discussion

In this case report, we present an aged DHL patient who accomplished a complete response to the management of 3 cycles of chemo-immunotherapy and CHM. The patient achieved a long-term complete remission and good quality of life over an 8-year follow-up under maintenance care of CHM. To the best of our knowledge, this is the first complete case report on DHL involving CHM. It is difficult to identify if the outcome was induced by chemo-immunotherapy or CHM use alone because the follow-up CT imaging was completed in May 2014 after these 2 interventions. Previous studies revealed that patients with DHL achieved lower rates of long-term progression-free survival (PFS) and overall survival (OS). A retrospective multi-centre study in 311 DHL patients with induction therapy and stem cell transplant showed that the PFS and OS were 10.9 and

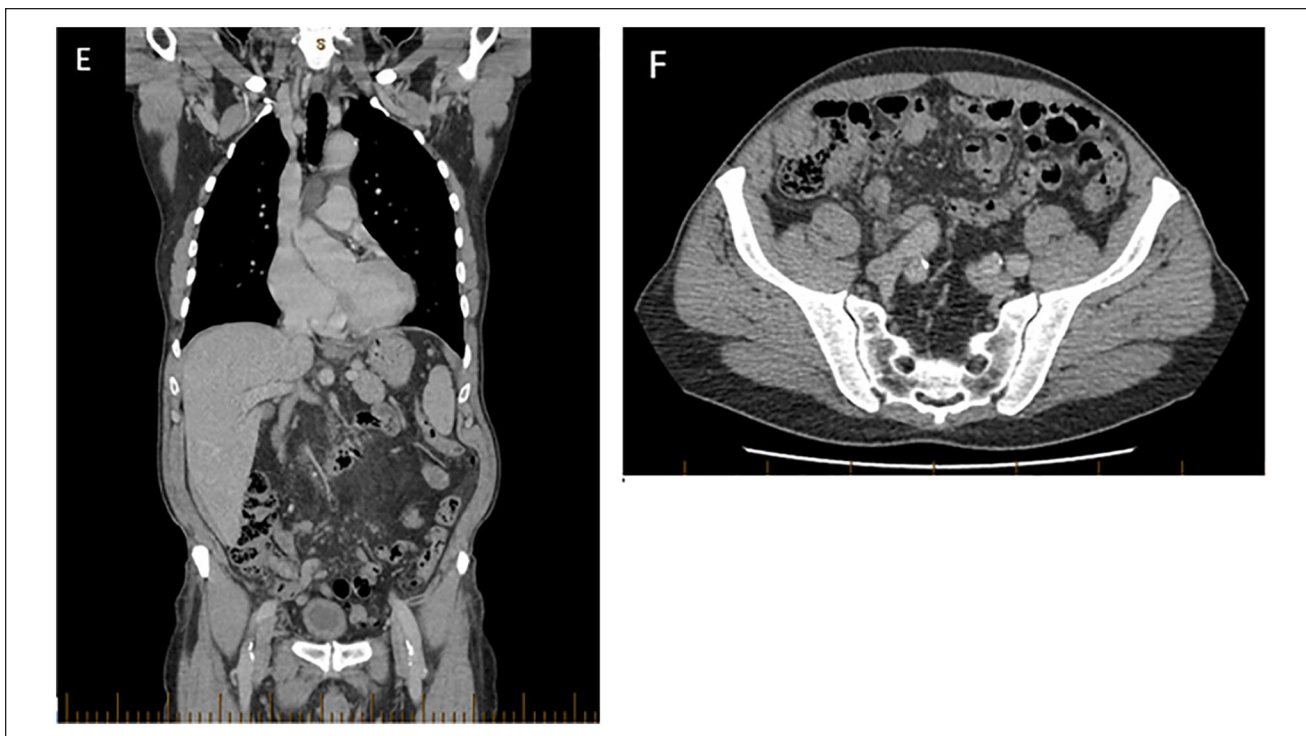


Figure 4. January 2018: no evidence of nodal recurrence (E and F).

21.9 months, respectively, with a median follow-up of 23 months.^{4,7} Furthermore, relapses are unfortunately common in DHL patients, and the outcomes for relapsed patients are generally very poor with survival averaging a few months.⁸ There were some relevant case reports. Markovic reported a 73-year-old male patient with double-hit primary unilateral adrenal lymphoma was treated with 6 cycles of R-CHOP chemotherapy.⁹ That patient was followed up regularly for 20 months with no evidence of tumor recurrence. This is a satisfying outcome, although no information on longer follow-up period. Another case of an 82-year patient with DHL was reported by Zaman et al.¹⁰ The patient initially received 3 cycles of R-CVP (Rituximab, Cyclophosphamide, Vincristine, and Prednisolone), but could not continue the intensive course of chemotherapy due to his compromised renal and blood parameters, and the patient died with the progression of the disease. Cheema presented with another DHL case of unusual response after sequential aggressive chemotherapies.¹¹ This was a man in his 50s with stage IIA DHL treated by R-Hyper-CVAD (rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine) but developed renal failure after the first cycle. The therapy was switched to R-ICE (rituximab plus ifosfamide, carboplatin, and etoposide) and induced complete remission. Unfortunately, the patient developed prolonged severe thrombocytopenia (grade 3) requiring a total of 4

units of platelet transfusion. By being treated with autologous hematopoietic cell transplantation (AHCT), he had a good tolerance and remained in complete remission for 1 year. These cases reveal that DHL has a poor prognosis and there is no accepted standard of treatment for DHL. The aggressive immunochemotherapy limits the outcome due to adverse effects or the intolerance of the patients. Comparatively, the present case demonstrates a positive outcome of a complete response by induced chemo-immunotherapy and Chinese herbal medicine as well as long-term survival with good quality of life. Therefore, the complete response in this case might be related to the integration of the chemo-immunotherapy in conjunction with CHM.

It is important to note that the patient had continually received 5-year CHM maintenance care which may benefit his outcomes of long-term disease-free and good quality of life. The basic prescription of CHM used in this case is a well-known formula known as *Sijunzi Decoction* (SJZ) including *Codonopsis pilosula*, *Atractylodes macrocephala*, *Poria cocos*, and *Glycyrrhiza uralensis*. SJZ-based adjuvant treatment to conventional chemotherapy significantly increased the overall response rate, as well as the 5-year OS, progression-free survival (PFS) and relapse-free survival (RFS) in lymphoma patients.¹² The SJZ-based formulation could also relieve nausea, vomiting and anemia caused by chemotherapy.¹² Numerous studies revealed that the underlying therapeutic mechanism of SJZ formulation is associated

with enhancing the body's immune functions in terms of increasing the levels of T cells and NK cells; IgA, IgG, and IgM; IL-2, IL-6, and IL-8; and TNF- α . In addition, this formula may act on induction of apoptosis and inhibition of tumor angiogenesis, tumor cell invasion, and metastasis.¹³ In the herbal granules used, the combination of *Astragalus membranaceus* and *Ligustrum lucidum* (AL) have been used for boosting immune functions and vital energy of cancer patients based on many pre-clinical and clinical research.¹⁴

Apart from SJZ and AL, some Chinese herbs with anti-cancer actions for lymphoma were added to the prescriptions for this case. *Prunella vulgaris* (PV) is a commonly used Chinese herb for lymphoma. A clinical study revealed that PV is an effective and safe herbal medicine for non-Hodgkin's lymphoma when used alone or adjuvant to chemotherapy.¹⁵ In vivo antitumor study demonstrated that the underlying anti-lymphoma mechanism of PV could involve increased expression of Bcl-2 protein and decreased expression of Bax protein, resulting in apoptosis of the lymphoma cells.¹⁶ *Sophora flavescens*, *Scutellaria baicalensis*, *Salvia miltiorrhiza*, and *Hedyotis diffusa* also demonstrate anticancer actions on malignant lymphoma. The possible anticancer mechanisms include suppressing the growth of lymphoma cells by inhibiting c-Myc and CDK6 oncogenes, and inducing cellular apoptosis by upregulating Bax proto-oncogene and cleavage of PARP nuclear enzyme.¹⁷⁻²⁰ Therefore, the value of the integrative application of CHM as a complementary and alternative intervention for DHL cannot be ignored, given there is currently no accepted standard of therapeutic agents for DHL.³ However, it should be pointed out that the results from a single case may not apply to patients in general. Further studies are warranted to investigate the efficacy and safety of specific CHM in managing DHL.

Conclusion

We report a unique case of a DHL patient, illustrating the potential values of CHM in inducing complete remission alongside chemo-immunotherapy, and maintaining long-term survival and satisfactory quality of life. The case report provides clinicians with preliminary evidence of the use of CHM as a therapeutic strategy in the management of DHL. Further investigations into the role of supportive care and maintenance therapy with Chinese medicine for DHL are worthwhile.

Declaration of Conflicting Interests

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Ethical Approval

This case report obtained an exemption from the human research ethics review approved by the Human Research Ethics Committee of Western Sydney University Australia (EX2021-01).

Informed Consent

Written consent was obtained from the patient for publication of this case report. A copy of the consent form has been submitted to the journal publisher.

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