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Contents

Thrice Monthly Volume 10 Number 21 July 26, 2022

OPINION REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Clinical and Translational Research

Case Control Study

Retrospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 21 July 26, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 21 July 26, 2022

Contents

CASE REPORT

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 21 July 26, 2022

Contents

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 21 July 26, 2022

Contents

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CASE REPORT

Refractory lymphoma treated with chimeric antigen receptor T cells combined with programmed cell death-1 inhibitor: A case report

Cang-Jian Zhang, Jun-Yu Zhang, Lin-Jie Li, Neng-Wen Xu

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Abstract

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is a common aggressive non-Hodgkin's lymphoma (NHL), accounting for 30%-40% of adult NHL. Primary testicular (PT) lymphoma is an uncommon extranodal disease representing approximately 1%-2% of lymphoma. Approximately 30%–40% of patients are refractory to frontline therapy or relapse after complete remission. Refractory DLBCL responds poorly to other lines of chemotherapy, and experiences short-term survival.

CASE SUMMARY

We present a 41-year-old male patient who was diagnosed with PT-DLBCL. Further disease progression was observed after multiline chemotherapy. Chimeric antigen receptor T cells (CAR-T) therapy salvaged the patient. Unfortunately, a new mass was observed in the right adrenal area after six months. The patient was administered programmed cell death protein-1 (PD-1) inhibitor therapy and maintained progression-free survival at more than 17 mo of follow-up.

CONCLUSION

Our findings support the potential benefit of CAR-T combined with PD-1 inhibitor therapies in this type of relapsed and refractory PT-DLBCL.

Key Words: Refractory diffuse large B-cell lymphoma; Programmed cell death protein-1 inhibitor; Chimeric antigen receptor T cells; Case report

Core Tip: Primary testicular diffuse large B-cell lymphoma (DLBCL) is an uncommon extranodal disease of lymphomas. Refractory DLBCL responds poorly to other lines of chemotherapy, and is associated with short-term survival. Herein, we report one rare case of chimeric antigen receptor T cells (CAR-T) combined with programmed cell-death protein-1 (PD-1) inhibitor to treat refractory DLBCL in a 41-year-old male. Our findings support the potential benefit of CAR-T combined with PD-1 inhibitor therapies in this type of refractory DLBCL.

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INTRODUCTION

Primary testicular lymphoma (PTL) is a rare lymphoma with a poor prognosis and poor response to conventional chemotherapy. PLT represents approximately 1%-2% of lymphomas[1]. Approximately 30%–40% of patients are refractory to frontline therapy or relapse after complete remission[2]. Chimeric antigen receptor T cells (CAR-T) have a significant effect on recurrent refractory lymphoma, with good effects on most clinical manifestations in the early stage but for a short duration. The use of programmed cell death protein-1 (PD-1) inhibitors improves tumor immunity in the microenvironment and the immune efficacy of CAR-T cells. It is unclear whether it has unique clinical and biological characteristics, and the therapeutic mechanism needs further study. Therefore, we report a case of primary testicular diffuse large B-cell lymphoma (PT-DLBCL) treated with a PD-1 inhibitor after CAR-T therapy. The clinicopathological characteristics and the mechanism of CRT-T combined with PD-1 inhibitor therapy are discussed based on relevant literature, which helps to improve clinical understanding.

CASE PRESENTATION

Chief complaints

A 41-year-old man with an 8-mo history of right testicular enlargement.

History of present illness

On June 29, 2018, he underwent right orchiectomy and right inguinal lymph node biopsy. He had no history of trauma, fever, or other complaints. Physical examination showed unilateral enlargement of the right testicle without any superficial lymph node enlargement. The patient received a right orchidectomy. The histopathological diagnosis of DLBCL (non-GCB) was rendered. Hematoxylin and eosin-stained sections showed diffuse proliferation of medium-sized round cells. Immunohistochemistry revealed that the neoplastic cells expressed CD19, CD20, CD79a, and CD21 and were negative for CD3, CD5, CD10, CyclinD1, and ALK. Ki-67 was positive in 80% of tumor cells. BCL-2 was positive in 80% of tumor cells. BCL-6 was partially positive. C-myc was positive in 60% of tumor cells (Figure 1). The patient was diagnosed with DLBCL (non-GCB) IV. On July 13, 2018, four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were given at the local hospital. A follow-up abdominal computed tomography (CT) scan showed that the lymph nodes continued to enlarge beside the right iliac vessels. On November 13, 2018, a positron emission tomography/CT (PET-CT) scan showed multiple enlarged lymph nodes (4.3 cm × 2.7 cm) beside the right iliac vessels (Figure 2A). Two cycles of R2-HyperCVADA (lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) were given. A treatment intensification strategy was applied, and second-Line R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) was administered. On July 15, 2019, a follow-up PET-CT scan showed that, in addition to the right iliac vessels, the lymph nodes continued to enlarge (4.3 cm × 3.8 cm) (Figure 2B).

History of past illness

His past medical history included diabetes and cervical spondylosis.

Personal and family history

No personal or family history was available.

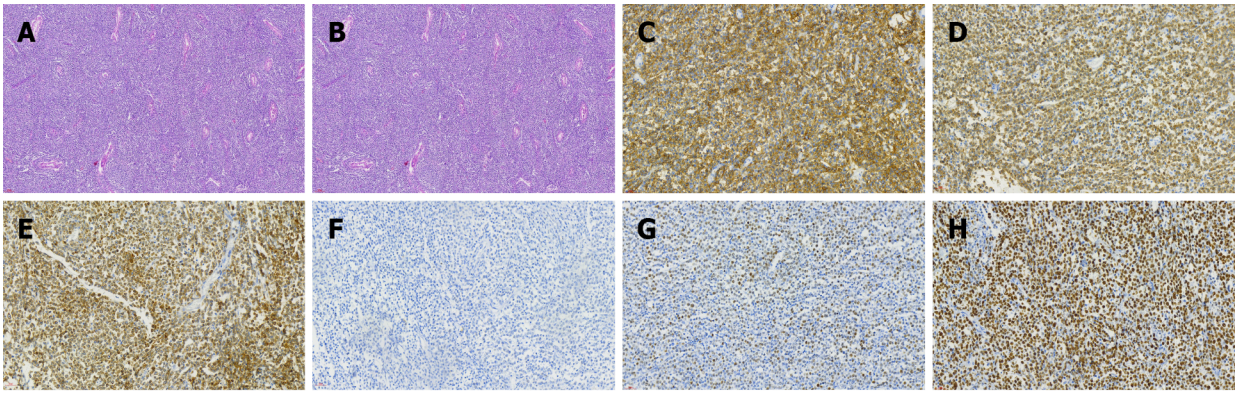

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Figure 1 Histopathological microphotograph of primary testicular diffuse large B-cell lymphoma. A: The basic structure of the testicle is destroyed, and there are a lot of lymphocytes infiltrating (magnification × 100); B: Hematoxylin and eosin stained sections showed diffuse proliferation of medium-sized round cells (magnification × 400); C-H: On immunohistochemistry, the neoplastic cells showed positive expression of CD20 (C), CD79a (D), BCL-2 (E), BCL-6 (F), C-myc (G); Ki67 staining showed almost 80% proliferation index (H).

Physical examination

Physical examination showed no palpable lymph nodes, organomegaly, or cutaneous lesions.

Laboratory examinations

The peripheral blood and biochemical parameters (liver and renal function and serum lactate dehydrogenase level) were within normal limits. Bone marrow (BM) smear and biopsy did not show evidence of involvement by lymphoma cells.

Imaging examinations

On November 13, 2018, a PET-CT scan showed multiple enlarged lymph nodes (4.3 cm × 2.7 cm) beside the right iliac vessels and a high standard uptake value (SUV) with a Deauville score of 18.4 (Figure 2A).

On July 15, 2019, a follow-up PET-CT scan showed that, in addition to the right iliac vessels, the lymph nodes continued to enlarge (4.3 cm × 3.8 cm). The SUV was high, with a Deauville score of 17. New viable lesions were found in the right adrenal gland, right seminal vesicle gland and surrounding prostate gland, and right groin (Figure 2B).

FINAL DIAGNOSIS

Based on the above findings, the final diagnosis was made as refractory PT-DLBCL, stage IVB.

TREATMENT

On July 24, 2019, the patient was transferred to the First Affiliated Hospital of Zhejiang University and treated with CAR-T cells at a dose of 5 × 10^6/kg. Lymph node size significantly reduced after CAR-T therapy. Unfortunately, in June 2020, an abdominal CT scan showed a new mass in the right adrenal area with a size of approximately 2.8 cm × 1.3 cm. On June 11, 2020, PD-1 blockade therapy with sintilimab (100 mg once every 3 wk) commenced. The mass shrank soon after the sintilimab injection.

OUTCOME AND FOLLOW-UP

A year later, a PET-CT scan showed no viable lesions (Figure 3). CAR copies were 9574.28 cells/L on July 6, 2021. He has maintained complete remission until now.

DISCUSSION

PTL is a hematological malignancy with a low clinical incidence of 0.26 cases *per* 100000 person-years [3]. PTL accounts for approximately 1%-7% of testicular malignancies and approximately 1%-2% of all

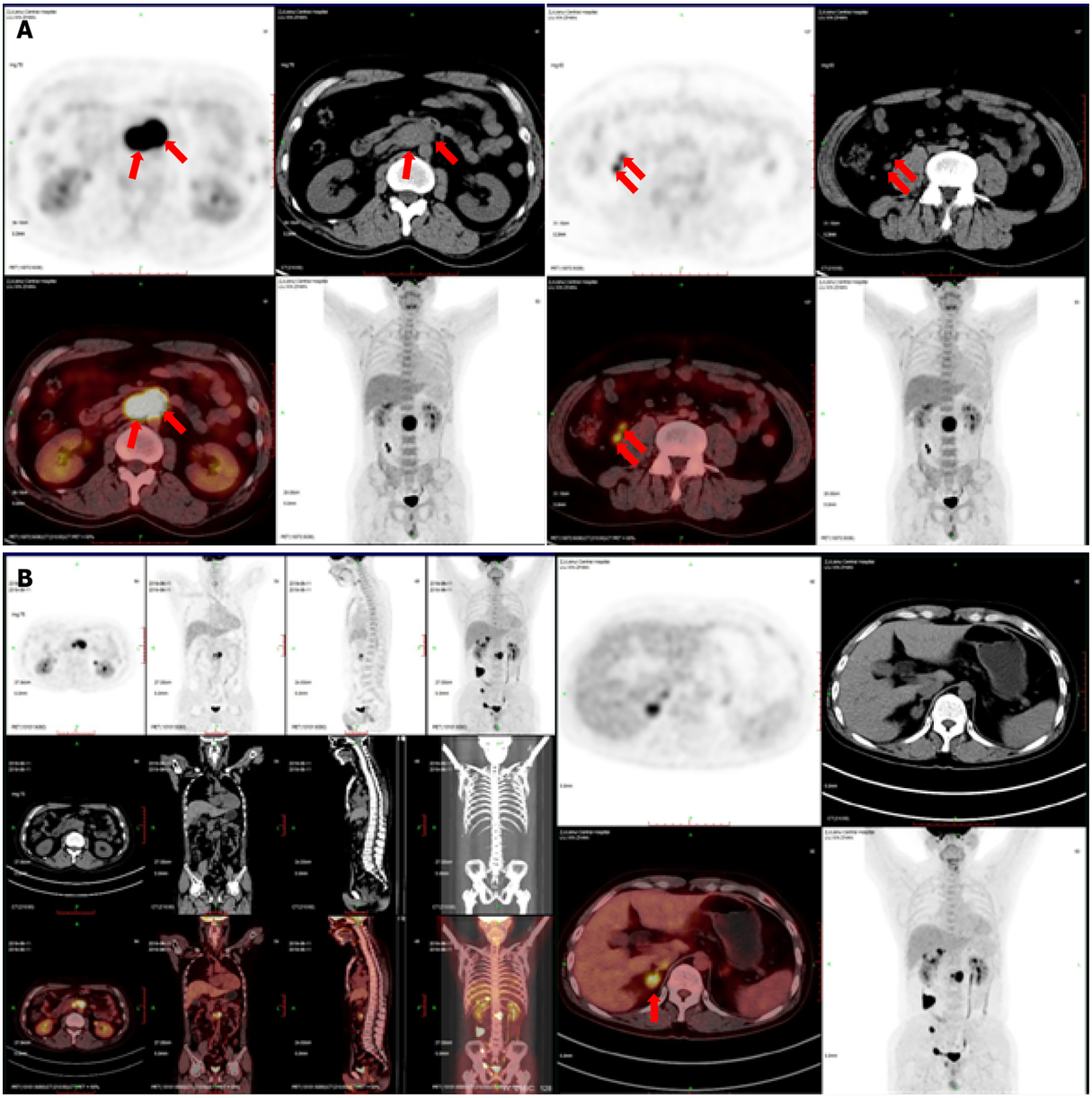

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Figure 2 Positron emission tomography/computed tomography scan. A: Positron emission tomography/computed tomography (PET-CT) scan showed multiple enlarged lymph nodes (red arrows); B: Follow-up PET-CT scan showed that, beside the right iliac vessels, the lymph nodes continued to enlarge. New viable lesions were found in the right adrenal gland, right seminal vesicle gland and surrounding prostate gland, and right groin.

lymphomas[1]. PTL is the most common lymphoma among males over 60 years of age. The most common histopathological DLBCL in PTL, which accounts for approximately 80%-90% of all PTLs, is called PT-DLBCL[4]. The primary clinical manifestation of PT-DLBCL is a painless enlargement of testicular tissue with occasional fever and night sweats, and weight loss. PT-DLBCL is highly aggressive and has a poor prognosis, with a median survival of 1-2 years, especially in patients with late clinical stages (stages III-IV), usually presenting with systemic multivisceral involvement within 2 years[5].

The clinical characteristics of PT-DLBCL are low incidence, high aggressiveness and complex treatment, which may explain the lack of a standard treatment at present. The recommended conventional treatment is chemotherapy after orchiectomy, which cures 60%-70% of patients[6]. However, a small number of patients have a poor response to treatment, with frequent recurrence and poor prognosis. Prognostic factors regarding testicular lymphoma have been suggested in several large retrospective reports[3]. In 2003, the International Extranodal Lymphoma Study Group suggested that advanced age, advanced stage, a high IPI score, elevated lactate dehydrogenase, and the absence of surgery or radiation therapy were significantly associated with poor prognosis[7]. In 2012, Richie[8] found that first-line treatment with R-CHOP, IT-MTX and testicular radiotherapy could improve the prognosis, while non-GCB cell phenotypes had a worse prognosis than GCB cell phenotypes[8]. In 2018, Ollila and Olszewski[9] found that patients with B symptoms, intranodal lymphoma, and concurrent

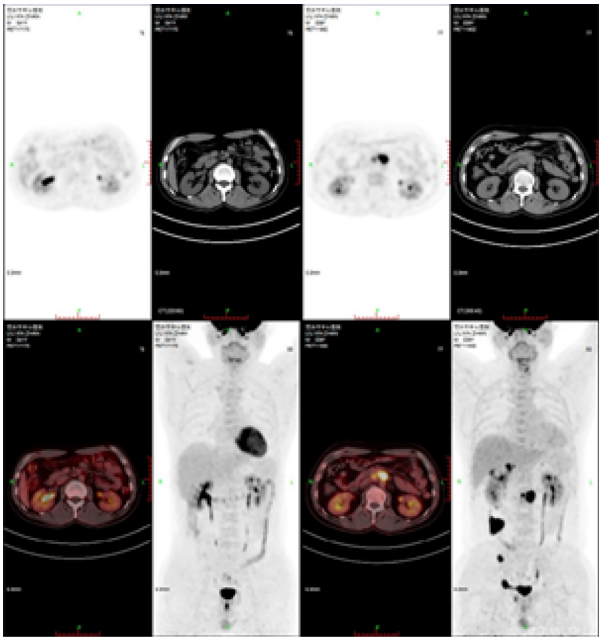

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Figure 3 After chimeric antigen receptor T cells combined with programmed cell death protein-1 inhibitor treatment, positron emission tomography/computed tomography scan showed no viable lesions.

MYC, BCL-2, or BCL-6 rearrangements ("double hit" or "triple hit") generally have a poor prognosis[9]. In this patient, advanced age, a high IPI score, elevated lactate dehydrogenase, and the fact that lymphoma persisted after multiple first-line chemotherapies suggested a poor prognosis. Therefore, second-line treatment can be selected according to 2021 NCNN guidelines[10], and CAR-T treatment can be given in combination with therapy depending on the patient's family's economic situation.

In recent years, there has been an increase in tumor immunotherapy use, especially CAR-T, which have been widely used to treat hematological tumors. CAR-T has an efficiency of approximately 80% and an OS rate of 52% at 18 mo in refractory large B-cell lymphoma[11]. The principle of CAR-T therapy is to genetically modify T lymphocytes to express a specific receptor (CAR) to target and bind specific antigens so that T cells can specifically recognize tumor cells and kill tumors[12]. In contrast to T cells under normal conditions, CAR-T cell recognition bypasses the antigen presentation phase. It thus is not restricted by MHC molecules, preventing cancer cells from escaping immune system recognition due to the downregulation of tumor MHC molecules[13]. CAR-T cell therapy can significantly improve the remission rate of relapsed refractory lymphomas, but some patients fail to achieve the desired outcome.

In the disease state, tumor cells upregulate the expression of immune checkpoints by immunosuppressive cells and bind to corresponding sites on T cells. This inhibits the killing activity of T cells and helps the cancer cells evade immune monitoring and attack from the body, thereby promoting their survival[14]. PD-1 is an immune checkpoint protein expressed on T cells. PD-1 binding to the receptor induces phosphorylation, which inhibits downstream activation of the T-cell receptor, limits T-cell proliferation activity and reduces its killing effect on tumor cells. In addition, the immunosuppressive effect of PD-1 Limits T cells. It affects the function of other lymphocyte subsets, such as promoting the proliferation and immunosuppression of regulatory T cells (Tregs) and inhibiting the activity of B cells and natural killer cells. Therefore, blocking the PD-1/programmed cell death ligand 1 (PD-L1) pathway increases the number of T cells and enhances cytokine secretion and reduces Treg cells and BM-derived suppressor cells to alter the inhibitory tumor microenvironment[15]. CAR-T cell therapy works by enhancing the antitumor capacity of T cells. The overexpression of immune checkpoints limits the lethality of T cells. Immune checkpoint inhibitors may enhance the efficacy of CAR-T cell therapy since the inhibition of immune checkpoint expression increases the antitumor ability of T cells. Studies such as that by Cherkassky proved that the inhibition of the PD-1 receptor could weaken the inhibition of the PD-1 pathway in CAR-T cells, thus enhancing the ability of CAR-T cells[16]. A study showed that PD-L1 expression was upregulated in hepatocellular carcinoma cells exposed to GPC3 CAR-T cells, and the antitumor activity of CAR-T cells could be enhanced by the knockdown of the PD-1 gene[17]. Chong *et al*[18] reported a patient with refractory and recurrent DLBCL. He received a PD-1 inhibitor 28 d after CAR-T cell treatment, after which the tumor cells shrank significantly. The patient was followed up for 12 mo, at which point sustained remission was achieved[18]. Wang *et al*[19] also reported a case of refractory follicular lymphoma (FL) treatment. After 6 cycles of chemotherapy, the patient was diagnosed with refractory FL, and the results were poor. The patient was treated with CD19 CAR-T cells in combination with a reduced dose of nivolumab. To date, the patient has maintained CR for 16 mo

Table 1 Pertinent literature

Ref.	Date	Sex	Age (yr)	Diagnosis	Response	Follow-up time (mo)
Chong *et al*[18]	2017	M	35	DLBCL	PR	12
Wang *et al*[19]	2019	F	70	FL	CR	10
Zhang *et al*[20]	2021	F	37	DLBCL	PR	17
Our case	2022	M	41	DLBCL	PR	12

M: Male; F: Female; FL: Follicular lymphoma; DLBCL: Diffuse large B cell lymphoma; PR: Partial complete remission; CR: Complete complete remission.

[19]. Zhang *et al*[20] showed a case of refractory DLBCL that developed disease progression after 12 wk of CAR-T cell treatment. Then, the patient was treated with a PD-1 inhibitor. To date, the patient has maintained CR[20]. Relevant literature reports were made by retrieving relevant literature at home and abroad (Table 1). In this article, the patient relapsed 6 mo after CAR-T cell therapy. PD-1 inhibitors were still effective, and CAR-T cells could still be detected in the patient 2 years later. These findings suggest that PD-1 inhibitors may affect the efficacy of CAR-T cell therapy in the tumor microenvironment of immune suppression.

CONCLUSION

CAR-T cells have been widely used to treat hematological malignancies, but their associated remission rates still need improvement. Immune checkpoint inhibitors can vastly alter the immunosuppressive microenvironment where CAR-T cells live, improving their proliferative activity and antitumor capacity and increasing the prognosis of relapsed refractory tumors. Even after the failure of CAR-T therapy, the choice of PD-1 inhibitor therapy may still be effective. Our center will continue to treat patients who have failed CAR-T therapy with PD-1 inhibitors to explore the therapeutic feasibility of this treatment option and to provide new treatment strategies for relapsed refractory lymphoma.

FOOTNOTES

Author contributions: Zhang CJ designed the report and wrote the paper; Li LJ collected the patient's clinical data; Xu NW analyzed the data; Zhang JY revised the paper; all authors have read and approved the final version of this manuscript.

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