



A case report of acquired immunodeficiency syndrome (AIDS)-related refractory Burkitt lymphoma got complete remission by multidisciplinary and multi-target combined therapy

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Background: The incidence of Burkitt lymphoma among acquired immunodeficiency syndrome (AIDS) patients is significantly higher than that in general populations. It often features high malignancy and a poor prognosis. For patients with AIDS-related Burkitt lymphoma, the guidelines recommend the dose-adjusted EPOCH-R (DA-EPOCH-R) regimen (rituximab + etoposide vincristine + doxorubicin + cyclophosphamide + dexamethasone) as one of the first-line treatment options. If complete or partial responses are not achieved after first-line treatment, then a second-line regimen such as rituximab + gemcitabine + dexamethasone + cisplatin (R-GDP) or rituximab + ifosfamide + carboplatin + etoposide (R-ICE) can be employed instead. Patients without response to the second line regimen often have poor prognosis. However, with our growing understanding of the pathogenic mechanism of Burkitt lymphoma, it has become apparent that patients with Burkitt lymphoma who have a poor response to first- and second-line regimens require personalized treatment, such as immune checkpoint inhibitors [programmed death 1 (PD-1) inhibitors] or new small-molecule inhibitors [e.g., Bruton tyrosine kinase (BTK) inhibitors: ibrutinib and zanubrutinib; B-cell lymphoma-2 (BCL-2) inhibitors: venetoclax]. For the efficacy of the personalized treatment, the publication is scarce.

Case Description: This report describes a patient with AIDS-related Burkitt lymphoma who did not achieve complete remission after first- and second-line treatment but eventually reached complete remission after combined therapy that included chemotherapy with small-molecule inhibitors, radiotherapy, and PD-1 inhibitors. During the multidisciplinary and multi-target combined therapy, patient has good tolerance. After 14 months' follow-up, patients' condition is stable.

Conclusions: In addition to traditional chemotherapy and radiotherapy, the combined use of novel targeted therapies and early anti-HIV treatment maybe a choice to improve the prognosis of patients with AIDS-related refractory Burkitt lymphoma.

Keywords: Acquired immunodeficiency syndrome (AIDS); Burkitt lymphoma; refractory; multi-target; case report

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Introduction

The incidence of lymphomas among human immunodeficiency virus (HIV)-infected patients is significantly higher than that in non-HIV-infected patients, regardless of whether they receive anti-HIV treatment (1).

Among these lymphomas, non-Hodgkin's lymphoma accounts for the vast majority of cases, with diffuse large B-cell lymphoma and Burkitt lymphoma being the most common types (2,3). The latter tends to be highly invasive, highly malignant, and difficult to treat, resulting in a poor

patient prognosis. A previous study reported that the 2-year survival rate for patients with acquired immunodeficiency syndrome (AIDS)-related Burkitt lymphoma is only 43% (4).

With the development of new antiviral drugs for AIDS, the prognosis of patients with Burkitt lymphoma is improving. The National Comprehensive Cancer Network (NCCN) guidelines recommend the dose-adjusted EPOCH-R (DA-EPOCH-R) regimen (rituximab + etoposide vincristine + doxorubicin + cyclophosphamide + dexamethasone) as one of the first-line treatment options for patients with AIDS-related Burkitt lymphoma. If complete or partial responses are not achieved following 2–4 courses of first-line treatment, then a second-line regimen such as rituximab+ gemcitabine + dexamethasone + cisplatin (R-GDP) or rituximab + ifosfamide + carboplatin+ etoposide (R-ICE) can be utilized instead. However, with our growing understanding of the pathogenic mechanism of Burkitt lymphoma, it has become apparent that patients with poor responses to first- and second-line regimens for Burkitt lymphoma require personalized treatment with new anti-lymphoma drugs, such as small-molecule inhibitors. The advantages of small-molecule inhibitors are gradually emerging. However, the publication focus on the efficacy of the personalized treatment is scarce.

The case reported in this study involves a patient with AIDS-related Burkitt lymphoma who did not achieve complete remission after first- and second-line treatment but reached complete remission after combined therapy that included chemotherapy with small-molecule inhibitors, radiotherapy, and programmed death 1 (PD-1) inhibitors. We present the following case in accordance with the CARE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-1375/rc>).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

The patient was a 29-year-old male. He had gingival swelling and pain with intermittent fever in March 2019. He received dental treatment but had no improvement. Thereafter, his symptoms became progressively aggravated. Two weeks later, he developed systemic bone and muscle

pain, especially in the shoulders and waist, a neoplasm on the left gingiva, swollen and painful bilateral cheeks, difficulty chewing (could only ingest fluid food), night sweats, and fatigue.

In May 2019, he was admitted to the Department of Stomatology for treatment. The gingival neoplasm was histopathologically diagnosed as a small round cell malignant tumour in the posterior area of the left molar, and lymphoma could not be excluded. The pathological results (provided by the Shanghai Public Health Clinical Center, Fudan University) were as follows: tumour cells—CD20⁺, PAX5⁺, BCL-2⁻, BCL-6⁺, MUM1⁺, CD3⁻, CD5⁻, CD21⁻, CD23⁻, CD30⁻, P53⁻, C-myc⁺ >90%, Ki-67⁺ almost 100%, and negative Epstein-Barr virus-encoded with small RNA (EBER) *in situ* hybridization. The pathological results, hematoxylin and eosin (HE) morphology, and immunohistochemical phenotype together indicated a malignant tumour of the lymphoid haematopoietic system (posterior area of the left molar), likely a Burkitt lymphoma [stage IV, International Prognostic Index (IPI) =3, medium-to-high risk]. 8q 24 (c-myc) translocation was detected using fluorescence *in situ* hybridization (FISH). In addition, the patient was positive for HIV antibodies in the initial screening, and HIV infection was confirmed by Western blot.

Positron emission tomography/computed tomography (PET-CT) performed on May 16 before admission (*Figure 1A,1B*) revealed the following: (I) multiple fluorodeoxyglucose (FDG) hypermetabolic bone lesions (including osteogenic and osteolytic lesions) throughout the whole body with thickening of the surrounding soft tissues and masses; high FDG uptake lesions in the sinuses, left thyroid gland, both lungs, chest, abdominal wall, pleura, peritoneum, liver, pancreas, gallbladder, bilateral renal cortex, perirenal area, left adrenal gland, prostate, and multiple sites at the gastrointestinal walls; FDG hypermetabolic bilateral testicular foci; and FDG uptake in multiple lymph nodes in the anterosuperior mediastinum, right internal mammary chain, abdominal cavity, mesenteric root, and right inguinal groin. (II) Irregular brain FDG metabolism, which was further evaluated by contrast-enhanced magnetic resonance imaging (MRI).

The physical examination on admission revealed redness, swelling, and tenderness of the left cheek, with no fluctuation, and a cauliflower-like neoplasm (1.5 cm × 1.0 cm) at the left molar, with local adhesions. A clinical test report on May 22, 2019, indicated a haemoglobin concentration of 96 g/L. The biochemical test results were as follows: aspartate aminotransferase, 48 U/L; alkaline

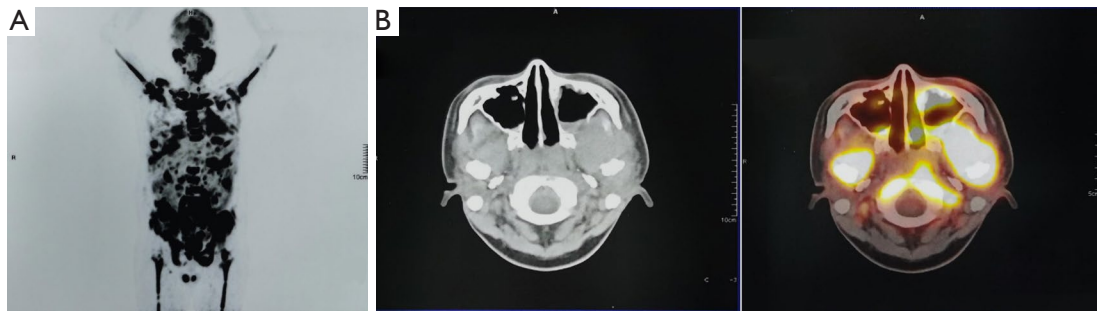


Figure 1 The PET-CT image before chemotherapy. (A) Whole-body PET-CT image at the time of lymphoma diagnosis. (B) PET-CT images of the bilateral cheek lesions at the time of lymphoma diagnosis. CT, computed tomography; PET, positron emission tomography.

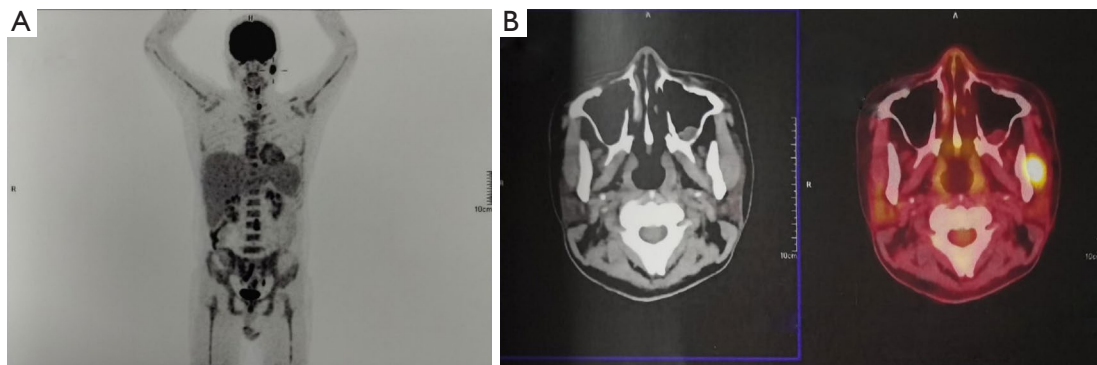


Figure 2 The PET-CT image after 4 rounds of EPOCH-R. (A) Whole-body PET-CT image after four rounds of systemic chemotherapy. (B) PET-CT images of the bilateral cheek lesions after four rounds of systemic chemotherapy. CT, computed tomography; PET, positron emission tomography; EPOCH-R, rituximab + etoposide vincristine + doxorubicin + cyclophosphamide + dexamethasone.

phosphatase, 1,070 U/L; L- γ -glutamyltransferase, 688 U/L; lactate dehydrogenase, 1,382 U/L; albumin; 23.5 g/L; uric acid; 748 μ mol/L; and C-reactive protein, 116 mg/L. The immunoassay report provided the following results: absolute CD8 count, 1,332 cells/ μ L; absolute CD4 count, 203 cells/ μ L; and CD4/CD8 ratio, 0.15. The HIV-RNA level was 2.75×10^4 copies/mL. Hepatitis B, hepatitis C, and syphilis antibody tests results were all negative.

After admission (May 22, 2019), the patient received highly active anti-retroviral therapy (HAART) [emtricitabine/tenofovir alafenamide (200 mg/25 mg po qd) + dolutegravir sodium (50 mg qd)]. The pain and swelling were slightly alleviated after pre-chemotherapy with steroids [dexamethasone (10 mg) iv qd] for 5 days as well as a single intravenous injection of vincristine (1 mg). The patient received the DA-EPOCH-R regimen, which is a first-line chemotherapy regimen (rituximab 375 mg/m², d0; etoposide 50 mg/m²/d, d1–d4, 96-hour continuous infusion; vincristine 0.4 mg/m²/d, d1–d4, 96-hour continuous

infusion; doxorubicin 50 mg/m²/d, d1–d4, 96-hour continuous infusion; cyclophosphamide 750 mg/m², d5; and dexamethasone 40 mg/d, d1–d5). This regimen was repeated every 21 days. During the chemotherapy period, 30 mg of cytarabine + 10 mg of methotrexate + 5 mg of dexamethasone was intrathecally injected four times. The patient's symptoms significantly improved after these treatments. There were no significant adverse effects about anti-HIV regimen, however, after EPOCH-R severe myelosuppression occurred. The nadir white blood cell was 0.23×10^9 /L, neutrophil granulocyte was 0.04×10^9 /L, and hemoglobin was 49 g/L. The granulocyte colony stimulating factor and red blood cells suspension were administered to relieve the adverse effect.

The PET-CT results on August 8, 2019, indicated a significant reduction in lesions (Figure 2A,2B). Some lesions were still active (tumour activity was observed in the left masseter, the small intestine near the right pelvic wall, the local jejunum at the level below the pancreatic tail, and the

left medial edge of the spinal canal at L3). Partial response was achieved through chemotherapy. Hence, a fifth round of chemotherapy was performed using the original regimen.

After September 9, 2019, the patient's left cheek swelled again, and the regimen was replaced with R-GDP, which is a second-line regimen (rituximab 375 mg/m², d0; gemcitabine 1,000 mg/m², d1, d8; cisplatin 75 mg/m², d1; and dexamethasone 40 mg, d1–d4). This regimen was repeated once every 21 days, and three rounds of chemotherapy were performed. During the chemotherapy period, intrathecal injections were performed twice. On October 22, 2019, the patient reported lumbar pain and received a lumbar spine magnetic resonance (MR) examination. The MR results revealed an intraspinal tumour at L2–3/L3–4, indicating lymphoma. On October 28, 2019, the patient received systemic chemotherapy with cytarabine (4 g) and an extra dose of methotrexate (4 g).

The patient had unrelievable low back pain, numbness in the lower limbs, decreased muscle strength (grade II), and urinary retention. Therefore, the regimen was changed to R-ICE + sintilimab (sintilimab 200 mg, d0; rituximab 375 mg/m², d0; etoposide, 100 mg/m², d1–d3; ifosfamide 5 g/m², d2; and carboplatin 800 mg, d2) starting on November 25, 2019. The patient's symptoms were not relieved after one treatment with this regimen. On December 4, the patient underwent neurosurgical treatment. The intraspinal tumour at L2–4 was resected. Postoperative muscle strength of the left lower limb was restored to grade IV, and the patient was able to lie supine.

On December 17, 2019, the R-ICE + sintilimab regimen was utilized again, with little effect on the left cheek mass. On January 10, 2020, the chemotherapy regimen was modified to R-ICE + sintilimab + ibrutinib (140 mg po qd). After 5 days, the patient's left cheek pain improved. The regimen was continued once every 3 weeks. After nine courses of treatment, PET-CT indicated complete remission; therefore, chemotherapy was discontinued. The sintilimab + ibrutinib regimen was continued as maintenance treatment.

After 6 weeks (September 9, 2020), the patient's left cheek swelled again, and his toothaches reoccurred; therefore, he was given local radiotherapy, five rounds of stereotactic body radiation therapy (SBRT) at 5.5 Gy, and sintilimab + ibrutinib + venetoclax (100 mg on d1; 200 mg on d2; 400 mg on d3; and then 400 mg daily for maintenance treatment). After treatment, the mass disappeared and the lesions improved. On March 1, 2021, due to congestion and oral mucosa ulcers, ibrutinib was replaced with zanubrutinib

(160 mg, po bid), and the regimen has not been modified since then.

The patient has been feeling well and has been receiving regular follow-ups and re-examinations. During the treatment process, biopsy tissues were subjected to second-generation sequencing, which showed primary mutations in *CREBBP/MYC/TP53*. The treatment process is summarized in *Figure 3*. Currently, the patient has no active lesions or clinical manifestations, with HIV-RNA <40 copies/mL and CD4 counts at 300–500/μL at the bi-annual re-examinations.

Discussion

The case reported in this study involved a patient with AIDS-related Burkitt lymphoma. The survival rate of this disease is low. A recent relevant study has concluded that although treatment efficacy has significantly improved, the overall survival rate of patients with AIDS-related Burkitt lymphoma is still significantly lower than that of non-AIDS patients or patients with AIDS-related diffuse large B-cell lymphoma (5).

Among the existing treatment regimens, DA-EPOCH-R is widely used in clinical practice due to its strong chemotherapeutic effects and good tolerance among patients. However, if patients do not respond to this regimen, a second-line regimen should be used instead. The patient in this study experienced tumour progression after treatment with the second-line regimen. According to the latest NCCN recommendation, in this situation, participation in clinical trials is recommended to obtain better treatment results. However, in areas with no access to clinical trials, an alternative approach is to use appropriate immune checkpoint inhibitors (including PD-1 inhibitors, such as sintilimab) or new small-molecule inhibitors (BTK inhibitors such as ibrutinib and zanubrutinib; BCL-2 inhibitors such as venetoclax; PI3K-δ and γ inhibitors; and PI3K-α and δ inhibitors).

In this case, ibrutinib (subsequently replaced by zanubrutinib due to adverse reactions) and venetoclax were administered. The former is a BTK inhibitor (6). As an important factor regulating signal transduction, BTK is a key component of the B-cell receptor (BCR) signalling pathway and plays an important role in the growth and differentiation of B cells. BTK is mainly expressed in B cells and myeloid cells and is distributed in the lymphatic, haematopoietic, and blood systems. Both *in vitro* and clinical experiments have shown that BTK is involved in signal transduction in B-cell malignancies, such as diffuse

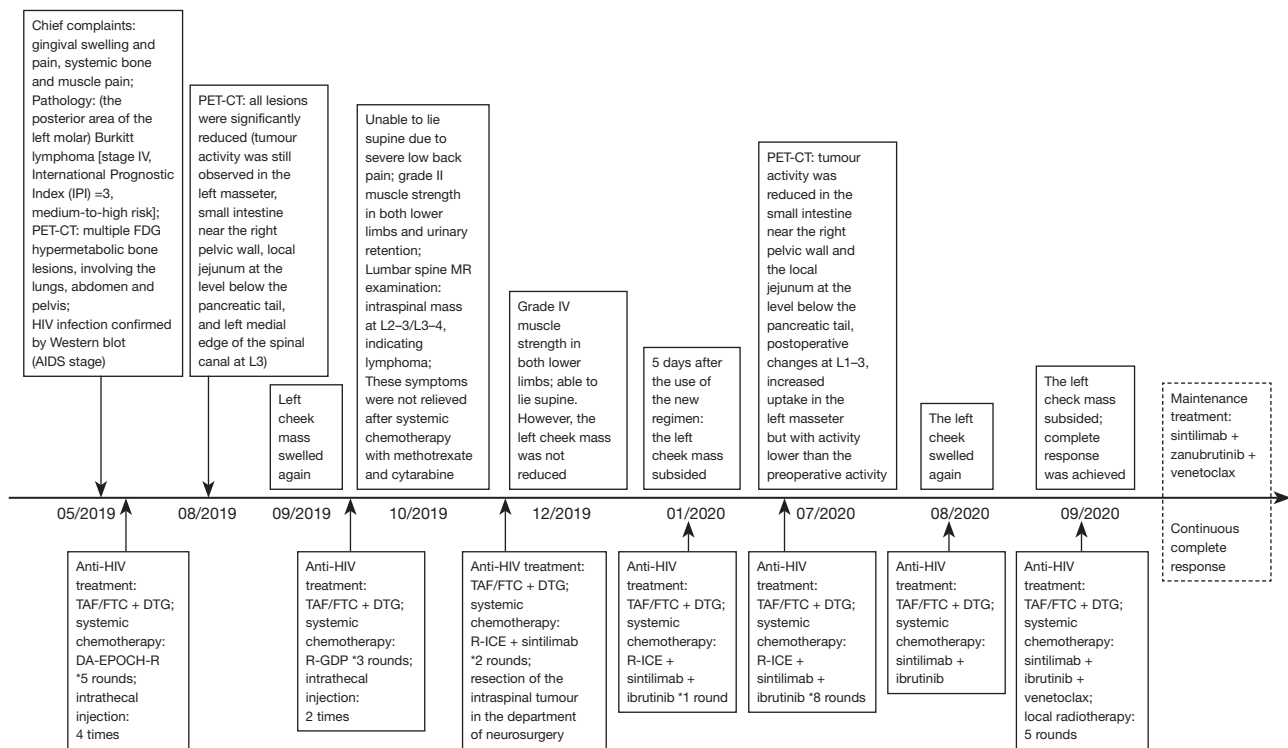


Figure 3 Overview of the patient's diagnosis, treatment, and condition changes. AIDS, acquired immunodeficiency syndrome; CT, computed tomography; HIV, human immunodeficiency virus; IPI, International Prognostic Index; PET, positron emission tomography; FDG, fluorodeoxyglucose; TAF, tenofovir alafenamide; FTC, emtricitabine; DTG, dolutegravir sodium; DA-EPOCH-R, dose-adjusted EPOCH-R (rituximab + etoposide vincristine + doxorubicin + cyclophosphamide + dexamethasone); R-GDP, rituximab + gemcitabine + dexamethasone + cisplatin; R-ICE, rituximab + ifosfamide + carboplatin + etoposide.

large B-cell lymphoma and chronic lymphocytic leukaemia. Ibrutinib can specifically bind to BTK, interrupt the B-cell signalling pathway, hinder the adhesion and migration of B cells, and ultimately cause B cell death (7).

BCL-2 plays an important role in apoptosis. It can prevent apoptosis in some cells (including lymphocytes) and is overexpressed in certain types of cancers, which is associated with the formation of drug resistance. As the first highly selective BCL-2 inhibitor approved for use in clinical practice, venetoclax can selectively inhibit the function of BCL-2, restore the cellular communication system, and kill cancer cells (8). The killing effect of venetoclax on susceptible cells is rapid and long-lasting because it efficiently induces tumour cell apoptosis by directly targeting proteins related to tumour cell apoptosis. After administration, the lymphoma proliferation pathway is inhibited, and the desired therapeutic effect can be achieved. Second-generation sequencing of the *TP53* gene in biopsy tissues from this patient indicated that the BCL-2 inhibitor

had good efficacy in TP53 refractory and recurrent chronic lymphocytic leukaemia. The combined use of venetoclax and a BTK inhibitor has been shown to achieve good efficacy for chronic lymphocytic leukaemia, mantle cell lymphoma, and diffuse large B-cell lymphoma (9-11). It should also be cautious to consider the interactions between anti-HIV agents and anti-lymphoma agents. For this case, we chose dolutegravir sodium (DTG) and tenofovir alafenamide (TAF) + emtricitabine (FTC) as the regimen for HIV treatment which has no drug-drug interaction with anti-lymphoma agents.

In addition, due to recurrent episodes of left cheek mass, we administered low-dose short-course radiotherapy and SBRT (5.5 Gy, five rounds). Radiotherapy involves the direct or indirect radiation of tumour cells, resulting in DNA damage and tumour cell death. However, it is now recognized that the induction of antitumor immune responses by radiotherapy also contributes to the antitumor effects (12). We used low-dose radiotherapy because high-

dose radiotherapy can lead to lymph node depletion and inhibit radiotherapy, leading to an immune response (13). A pooled analysis showed that compared with pembrolizumab alone, SBRT combined with pembrolizumab has significant benefits in improving the tumour response rate, overall survival, and progression-free survival (14). Radiotherapy has been redefined as a partner for cancer immunotherapy, with potential synergistic effects. During the follow-up of this case, the treatment related adverse reactions were not significant.

Currently, medication choice and cost are serious challenges for the treatment of AIDS-related Burkitt lymphoma. To obtain better treatment outcomes, the scope of testing should be expanded, and more new targeted therapies should be utilized. The early diagnosis, detection, and treatment of HIV infection may be another preventive measure.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-1375/rc>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-1375/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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