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Case Report

Successful treatment of hemophagocytic intravascular large B-cell lymphoma with CNS involvement with BTK inhibitor combined with rituximab and high-dose methotrexate

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***Abstract*:** This is a case of hemophagocytic intravascular large B-cell lymphoma (IVLBCL) with central nervous system (CNS) involvement. Although R-CHOP chemotherapy regimen has been shown significant improvement in survival rate. The prognosis and outcomes remain unsatisfactory, which is identified as outstanding challenges and need solutions. Gene and molecular profiling studies may provide new therapeutic strategies, especially the BCR/TLR/IL-1R/NF-κB signaling pathway in IVLBCL. Here, we treated the hemophagocytic IVLBCL CNS-involved patient with the Bruton tyrosine kinase inhibitor (BTKi) to block NF-κB pathway, and indicated that the second-generation BTKi zanubrutinib-based treatment was feasible and efficient.

Keywords: BTK inhibitor, CNS involvement, hemophagocytic syndrome, intravascular large B-cell lymphoma, NF-κB pathway

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive subtype of extranodal diffuse large B-cell lymphoma (DLBCL) that grows selectively within the lumen of blood vessels, particularly capillaries. Lacking obvious tumor mass or lymphadenopathy and the difficulties of obtaining sufficient patient samples contribute to the challenge for making a timely and accurate diagnosis of IVLBCL. Three distinct patterns of clinical presentations of IVLBCL have been described (i.e., classic, cutaneous, and hemophagocytic). The western variant predominantly involves skin and the central nervous system (CNS), especially as a "cutaneous variant" limited to the skin. The asian variant often presents with hemophagocytic syndrome leading to hepatosplenomegaly, pancytopenia, and multiorgan failure.[1]

Although the addition of rituximab to the conventional CHOP chemotherapy regimen in patients with IVLBCL has been shown significant improvement in complete remission rates, event-free survival, and overall survival.[2] The prognosis remains unsatisfactory, especially for CNS involvement and hemophagocytic syndrome, which has been identified as unfavorable risk factors in patients with IVLBCL.[1] Recent studies have identified the prevalence of mutations in genes involved in BCR/TLR/IL-1R/NF-κB signaling pathways in IVLBCL.[3,4] It is rationale to question whether patients with IVLBCL may benefit from targeted treatment with the Bruton tyrosine kinase inhibitor (BTKi) that blocks the NF-κB pathway. Here, we presented a middle-aged and elderly patient with hemophagocytic IVLBCL with CNS involvement and indicated

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that the second-generation BTKi zanubrutinib-based treatment was feasible and efficient. The patient gave his written informed consent.

Case presentation

A 69-year-old man was admitted to the hospital after a 1-week history of unusual headache, dizziness, and chills. At examination, he was febrile (39.2°C). Blood tests revealed increased C-reactive protein level (88.3 mg/L, normal range (NR) <6.0 mg/L). Brain computerized tomography (CT) scan showed low-density changes in the left frontal lobe (Figure 1(a)). The patient was first suspected to have intracranial infection or cerebral infarction with hemorrhage. However, his condition progressed worse and the antibiotics treatment resulted in poor response. One day after hospitalization, he suffered from chest tightness and shortness of breath, and was unable to maintain blood oxygen saturation. He developed respiratory failure and was sent to intensive care unit (ICU) for monitoring and further treatment.

The patient had no pulmonary embolism, pleural effusion, or cardiac dysfunction, but only mild interstitial pneumonia. He had no special medical, family, and psychosocial history.

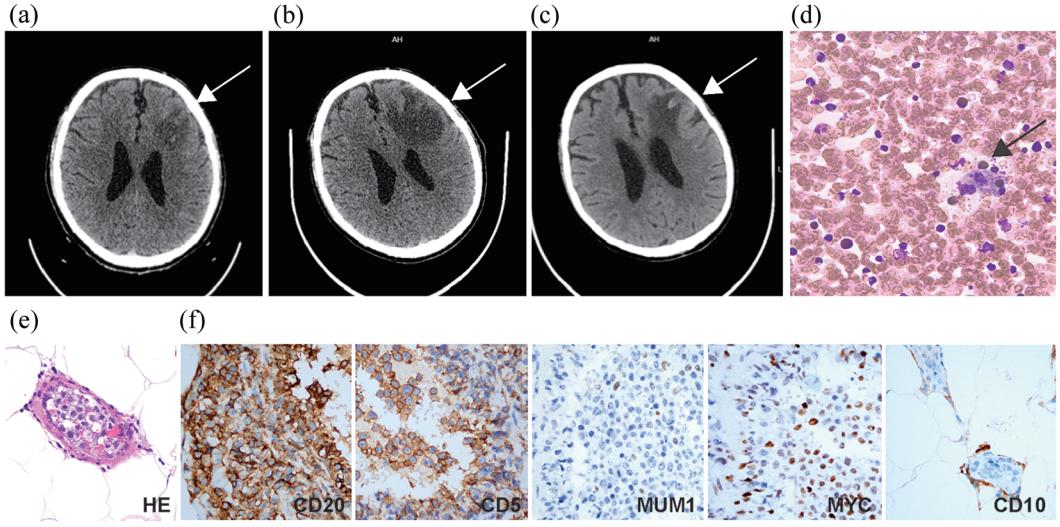
He started to experience a variety of neurological symptoms in day 2 in ICU, including aphasia, personality changes, cognitive decline, and impaired consciousness. He was treated by intubation and mechanical ventilation because of respiratory failure. Re-examination of CT imaging indicated that the lesions in the patient's brain continued to progress (Figure 1(b)). CT of his brain showed the small hematoma in the left frontal lobe accompanied by edema with finger size. Taking into account that frontal lobe was not the common bleeding site of brain, other possible causes were considered, such as cancer metastasis, brain abscess accompanied by hemorrhage, and vascular diseases. Cerebrospinal fluid (CSF) detections, including ink staining, gram staining, acid resistance staining, bacterial and fungal culture, and next-generation sequencing (NGS) for pathogenic microorganism all were negative. CSF detection for autoimmune encephalitis was negative. White blood cell count was 2/mm^3 (2/mm^3 < NR < 8/mm^3), and no red blood cells were detected in CSF. Normal level of glucose (3.7 mmol/L, 2.50 mmol/L < NR < 4.44 mmol/L), chloridum (129 mmol/L, 119 mmol/L < NR < 129 mmol/L), and microalbumin (401.9 mg/L, 150 mg/L < NR < 450 mg/L) were detected in CSF. None tumor cell was found in pathology detection of CSF.

He had normal counts of red blood cells, white blood cells, and platelets at disease de novo, but later developed anemic (hemoglobin 101 g/L) and thrombocytopenic (54×10^9/L) with an elevated lactate dehydrogenase of 1942 U/L (NR < 250 U/L). Hypertriglyceridemia (6.02 mmol/L, NR < 1.7 mmol/L), hyperferritinemia (750 μg/L, NR < 400 μg/L), elevated levels of soluble CD25 (16,737 pg/mL, NR < 6400 pg/mL), and diminished NK cell activity (14.82%, NR > 15.11%) were detected in his peripheral blood sample. The bone marrow aspirate showed 1.5% hematophagocytes lacking obvious evidence of neoplastic or infectious disorders (Figure 1(d)). Detection of hematological malignancies by flow cytometry for peripheral blood sample and bone marrow aspirate were negative. He was diagnosed with secondary (acquired) hemophagocytic syndrome according HLH-2004 diagnostic criteria.[5]

The patient also received other various examinations. Rheumatic immunity indexes of antinuclear, anti-dsDNA, anti-SSA, and anti-SSB were negative. Complement C3 and C4 levels were normal. Galactomannan detection, (1-3)-β-D-glucan detection, and respiratory virus antibody were negative. Globulin level was 30.4 g/L (25 g/L < NR < 35 g/L). The levels of HIV antibody, EBV-DNA, and CMV-DNA were normal. Applying NGS detection panel for pathogenic microorganisms including 11,027 species of bacteria, 11,704 species of viruses, and 1324 species of fungi, 0.14% abundance of aspergillus niger was detected in the patient's bronchoalveolar lavage fluid sample.

No tumor cell infiltration was detected in lymph node biopsy.

Taking into account that hemophagocytic syndrome is mainly secondary to an underlying malignancy, typically a primary hematological neoplasm. Subsequently a random skin biopsy was performed and found that a B-lymphocyte population with pleomorphic nuclei and prominent nucleoli expanded in dermal blood vessel



(g)

genes	genetic variant	protein effect	exon location	mutation type	mutation ratio
KMT2A	c.9635C>T	p.T3212I	exon27	missense	3.24%
IRF8	c.271G>A	p.D91N	exon3	missense	17.48%
STAT3	c.719T>C	p.L240P	exon8	missense	3.35%
NOTCH2	c.6449_6450del	p.P2150Rfs*2	exon34	frameshift	3.38%
BCL6	c.148C>T	p.L50F	exon3	missense	2.19%
CCND3	c.869T>C	p.I290T	exon5	missense	7.81%
BRAF	c.1780G>A	p.D594N	exon15	missense	4.29%
CARD11	c.2212T>C	p.W738R	exon17	missense	7.8%

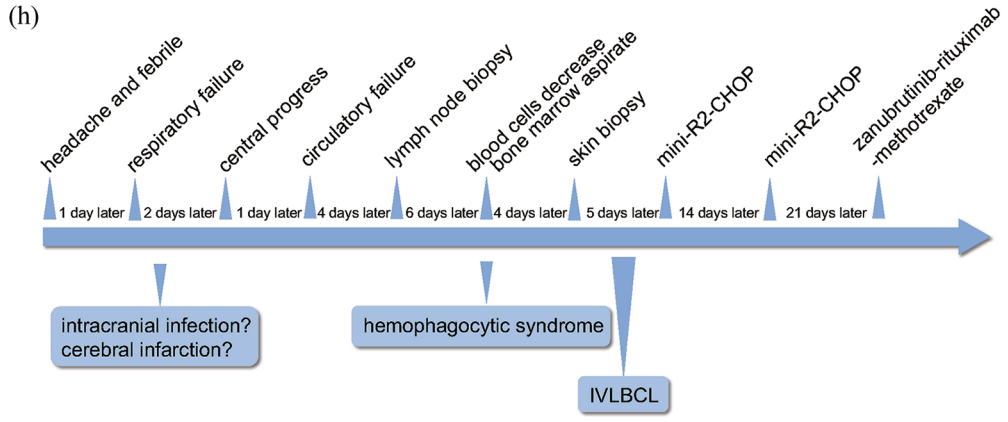


Figure 1. Summary of laboratory findings and clinical course. CT images of IVLBCL cerebral lesion in the left frontal lobe obtained on admission (a), in disease progression (b). (c) The reduced lesion was detected on CT imaging of the patient's brain after three cycles of chemotherapy. (d) Hematophagocytes in bone marrow image (hematoxylin-eosin, ×400). (e) Hematoxylin and eosin staining showed lymphoid cells with pleomorphic nuclei and prominent nucleoli selectively accumulated within the small vessel (hematoxylin-eosin, ×400). (f) Immunohistochemical staining for CD20, CD5, MUM1, C-Myc, and CD10 revealed that lymphoid cells were positive for CD20, C-Myc, and CD5, negative for MUM1, and CD10 (×400). Samples from deep ham skin biopsy showed small and medium vessels. (g) List of mutated genes detected in the lymphoma cells using next-generation sequencing. (h) The graphical timeline of the diagnostic process and treatment.
CT, computerized tomography; IVLBCL, intravascular large B-cell lymphoma.

(Figure 1(e)). No tumor cell was detected in extravascular location. Immunohistochemical studies showed the lymphoma cells were positive for CD20, CD5, CD31, BCL2, BCL6, and C-Myc, while negative for CD3, CD30, CD10, MUM1, Cyclin D1, PD-L1, and TDT (Figure 1(f)).

The patient was finally diagnosed as hemophagocytic IVLBCL (Figure 1(h)), belonging to germinal center B cell-like subgroups.[6] Owing to the mini-CHOP was more tolerable for the elderly patient with severe comorbidities, he began to receive chemotherapy with two cycles of mini-R2-CHOP (Rituximab 375 mg/m^2 on day 0, Cyclophosphamide 400 mg/m^2 on day 1, Vindesine 2 mg on day 1, Doxorubicin hydrochloride liposome 25 mg/m^2 on day 1, Prednisone 40 mg day 1–5, Lenalidomide 25 mg for 10 days) with a 14-day interval. To discover whether the patient has opportunities to receive new target-drug therapy, a customized NGS panel using Illumina Next 500 to target single nucleotide variations and insertion-deletions in 188 lymphoma-related genes including key gene signatures of B-cell differentiation, oncogenic signaling, the tumor microenvironment, and genes related to chemotherapy drug with side effects (Supplemental Table S1) was performed in the skin biopsy sample. Missense or frameshift mutations across *KMT2A*, *IRF8*, *STAT3*, *NOTCH2*, *BCL6*, *CCND3*, *BRAF*, and *CARD11* genes were identified (Figure 1(g)).

Taking into account the better BBB barrier permeability of the second-generation BTKi zanubrutinib,[7] we chose zanubrutinib combined with rituximab and methotrexate as following treatment regimen (Rituximab 375 mg/m^2 on day 0, Methotrexate 3.5 g/m^2 on day 1, Zanubrutinib 80 mg for 10 days). The patient had pulmonary fungal infection and took voriconazole orally simultaneously, the dose of zanubrutinib was reduced to 80 mg daily. The antitumor effect was excellent. His cognitive function, ability of speech, and action had improved and was extubated. The obvious improvement was seen in brain CT evaluation after three cycles of chemotherapy (two cycles of R2-miniCHOP, one cycle of zanubrutinib + rituximab + high-dose methotrexate (HD-MTX)). The brain lesion became smaller and edema reduced (Figure 1(c)). It has been reported that the most common adverse effects of zanubrutinib-based regimens were neutropenia, thrombocytopenia, infection, nausea, vomiting, abnormal alanine transaminase, and mucositis.[7] The patient experienced grade 3 neutropenia and anemia after chemotherapy, but recovered before the next cycle of chemotherapy began. No tumor dissolution, arrhythmia, hemorrhage, thrombosis, or rash occurred. His platelets was low before treatment (33×10^9/L), and recovered to normal after chemotherapy. At the moment of writing, the patient was in good clinical condition and had a good performance status.

Discussion

The hemophagocytic type of IVLBCL has the dismal outcome with median survival of 2–8 months compared with those of the cutaneous type or the classic type of IVLBCL.[8] R-CHOP was the standard treatment for non-CNS-IVLBCL.[1,9] The challenge for treatment was that the majority of patients finally experienced lymphoma relapse in CNS, no matter the patients had CNS infiltration at diagnosis or not. Study showed that addition of rituximab to CHOP did not significantly decrease the risk of CNS recurrence.[10] So treatment and prophylaxis for CNS disease are an important part of the tumor management. To date, few data on the optimal treatment for CNS-IVLBCL were published. In CNS-involved IVLBCL patients, R-CHOP combined with BBB-penetrating drug HD-MTX and intrathecal chemotherapies is the usual recommended treatment.[9]

In order to explore advances in treatment strategies, the genomic landscape of IVLBCL was elucidated by whole-exome sequencing.[3,4] The IVLBCL associated dysregulated molecular pathways mainly included BCR/NF-κB, immune escape, chromatin remodeling, cell cycle, and others. NF-κB activation was a dominant downstream pathway to maintain B-cell viability. *MYD88 L265P* mutation and *CD79B Y196* mutation were the major mutations, resulting in NF-κB signaling pathway over-activation and promoting cell survival.[4,11] CD79B induces the activation of NF-κB signaling through BTK. DLBCL patients with *MYD88* and/or *CD79B* mutations could achieve good therapeutic effect with BTKi, such as ibrutinib, to block NF-κB signaling.[12] Furthermore, it has been reported that *CD79B* mutations significantly improved the survival of DLBCL patients with *MYD88 L265P*-mutant ABC subtype, which is speculated to be linked to

the increased surface BCR expression and BCR signaling induced by *CD79B* mutations and could be inhibited by rituximab.[11]

The patient in our case was hemophagocytic type of IVLBCL with CNS involvement, which has the most dismal prognosis. In order to improve the patient survival possibility, we performed target gene sequencing involved 188 lymphoma-related genes. Missense or frameshift mutations of *KMT2A*, *IRF8*, *STAT3*, *NOTCH2*, *BCL6*, *CCND3*, *BRAF*, and *CARD11* were identified. These mutations were involved in RAS/RAF/MEK/ERK/MAPK, NOTCH, JAK/STAT, and BCL6 signaling pathway as well as epigenetic regulation and cell cycle. Although the common mutations of *MYD88 L265P* and *CD79B Y196* were not detected in our case. *IRF8* gene mutated at *p.D91N* site and *CARD11* gene mutated at *p.W738R* site were detected, which was also involved in BCR/NF-κB signaling pathways. IRF8 inhibited NF-κB signaling pathway by targeting MYD88.[13] CARD11 acted as the downstream of BTK and activated NF-κB pathway. It is worth noting that lymphoma cells harboring *CARD11* coiled-coil domain mutants were resistant to BTKi such as ibrutinib.[14,15] While *CARD11* mutation at *p.W738R* site detected in our case was outside the coiled-coil domain and not involved in the known resistant structures. As the first-generation BTK inhibitor, ibrutinib has shown its high BBB penetration ability and associated with superior survival.[16] The excellent BBB penetration of zanubrutinib was also confirmed. After adjustment, the CSF/plasma ratio of zanubrutinib increased to nearly 40%,[7] compared with CSF/plasma ratio of 28.7% in ibrutinib.[12] Some studies reported successful cases of refractory CNS lymphoma treated with zanubrutinib.[17,18] However, there is no clinical evidence of zanubrutinib in CNS-IVLBCL. We first use BTKi zanubrutinib-based treatment for IVLBCL, and the promising results on the effect of BTKi-based therapy might present a proof-of-principle for patients with IVLBCL, and therefore, patients with the disease need to be included in future studies.

On the other hand, published studies demonstrated that immune evasion also played important roles in IVLBCL pathogenesis.[19] Consistent with the reports in various cancers, IVLBCL harbored *PD-L1/PD-L2* rearrangements behaving as molecule overexpression, coupled with frequent deletions and mutations of HLA molecules, which were the important components of the immune escape armament in IVLBCL. IVLBCL with high-expression of PD-L1/PD-L2 might benefit from PD-1/PD-L2 blockade. However, our patient's lymphoma cells were negative for PD-L1/PD-L2 rearrangements and had low of PD-L1/PD-L2. So our patient may be unlikely to benefit from immune checkpoint inhibitors.

In conclusion, the present therapeutic options for IVLBCL remain limited. In particular, IVLBCL with CNS involvement highlighted the poor outcome and needed more specific ways of exploiting lymphoma-targeting treatment as well as BBB-penetrating drug. In the future, focusing on genetic and epigenetic alterations analyses of IVLBCL and large prospective trials for development of novel targeted should be conducted to address this issue.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University School of Medicine [approval number: No. 20210210-178].

Consent for publication

Written informed consent was obtained from the patient and the guardian.

Author contributions

Fangfei Shao: Conceptualization; Data curation; Methodology; Writing – original draft.

Wei Su: Conceptualization; Data curation; Methodology; Writing – original draft.

Xiujie Zhao: Data curation; Writing – review & editing.

Jianping He: Data curation; Writing – review & editing.

Xiaofen Wang: Data curation; Writing – review & editing.

Feng Guo: Project administration; Supervision; Writing – review & editing.

Haowen Xiao: Project administration; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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