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Case Presentation

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Brentuximab Vedotin in Combination with Rituximab, Ifosfamide, Doxorubicin Hydrochloride, and Prednisone Chemotherapy for Lung Gray Zone Lymphoma: A Case Report and Mini-Review

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Abstract

Background: Gray zone lymphoma (GZL), as B-cell lymphoma, cannot be classified yet and has characteristics between diffuse large B-cell lymphoma and classical Hodgkin's lymphoma (BCLu -DLBCL/ cHL). Gray zone lymphoma is often challenging to diagnose, and there is no consensus on the best treatment options, and it typically involves the mediastinum in young males. The 62nd American Society of Hematology analyzed the efficacy and safety of BV combined with Nivo in treating relapsed or refractory mediastinal gray zone lymphoma (MGZL), making BV combined with other drugs a potential treatment option. Currently, most reported cases of GZL occur in Caucasian and Hispanic individuals, with a lower incidence in Asian populations, including Chinese populations.

Case summary: A 28 - year-old female visited our hospital's Department of Respiratory Medicine because of repeated cough, expectoration, and bloody sputum without obvious inducement. There was persistent acupuncture-like pain in the left chest and back, and the pain aggravated when breathing, moving, and pressing. Afterward, she coughed up dark red bloody sputum in the morning, and the amount of hemoptysis throughout the day was about 10mL. Contrast-enhanced computed tomography (CT), and 18F-Fluorodeoxyglucose Positron Emission Tomography (PET)/ computed tomography (CT) showed multiple lesions in her left lung (mainly in the left upper lobe). Laboratory tests showed blood routine WBC 7.01×109/L, NEU 5.054×109/L, HGB 107g/L, PLT 281×109/LCRP 1.05mg/L, immunophenotype [CD20+, CD3-, CD30+, PAX5+ / 1, CD15+, ALK1-, CD117-, Ki67 about 50%, the pathological diagnosis was gray zone lymphoma (GZL). After left upper

lobectomy, the patient received Brentuximab vedotin, Rituximab, ifosfamide, doxorubicin hydrochloride, and prednisone chemotherapy because the tumor cells were CD30 positive and achieved complete remission (CR) clinically and impactologically.

Conclusion: The diagnosis of GZL is based on histopathological and immunophenotyping. BV-R-CHP chemotherapy is an effective treatment.

Keywords: Classical hodgkin lymphoma; Diffuse large B- cell lymphoma; Gray zone lymphoma; BV-R-CHP; Case reports

Introduction

Gray Zone Lymphoma (GZL), as B-cell lymphoma, which cannot be classified, and has characteristics between diffuse large B-cell lymphoma and classical Hodgkin's lymphoma (BCLu -DLBCL/cHL) **[1-4].** It was first recognized in the WHO lymphoma classification in 2008 **[5].** It is clinically rare and complex in diagnosis and treatment **[6].** It usually occurs in men aged 20-40 **[1].** Clinically, it mostly starts with a large mass in the anterior mediastinum, which can involve supraclavicular lymph nodes and thymus; it can also start outside the thymus, directly invade the lungs, and spread to the Liver, spleen, bone marrow, etc. **[7].** Moreover, compared with Primary Mediastinal large B-Cell Lymphoma (PMBL) or Classical Hodgkin's Lymphoma (cHL) has a more aggressive clinical course, a worse prognosis, and is often fatal **[8].** Here, we report the case of a patient with GZL, which is rare in Asian populations, who successfully received CD30, Rituximab, ifosfamide, doxorubicin hydrochloride, prednisone (BV-R-CHP) chemotherapy.

Case Presentation

A 28-year-old female was referred to the Department of Respiratory Medicine of our hospital because of recurrent cough, expectoration, and bloody sputum without obvious inducement. Admission examination: persistent acupuncture-like pain on the left chest and back, aggravated pain when breathing, moving, and pressing aggravated symptoms, and coughed up dark red bloody sputum in the morning, and the amount of hemoptysis throughout the day was about 10mL, without chills, chills, fever, dyspnea, cyanosis of the lips, orthopnea, lower extremity edema, etc.

Laboratory tests: blood routine WBC 7.01×109/L, NEU 5.054×109/L, HGB 107 g/L, PLT 281×109/L, CRP 1.05 mg/L, no abnormalities in liver and kidney function indicators; LDH: 194 IU /L, Epstein-Barr virus: <5*10 3 /ml.

Immunohistochemistry: Tumor cell immunophenotype [CD20+, CD3-, CD30+, PAX5+/1, CD15+, ALK1-, CD117-, Ki67 about 50%] ; other immunophenotypes [CK-, CK7-, TTF1-, CD21 -, PAX8-, SALL4-, P63, S100, CD58-; ISH: EBER1/2-] Complementary immune phenotype [MUM1+/-, OCT2-, EMA-, CD101, BCL2+/1, BCL6-, P53+/ About 5%, CD5-, MYC-]; proliferating lymphocytes supplemented by immunohistochemistry [CD19 (part of cells +), CD79a (part of cells +), CD23 (-), PD1 (-)].

Imaging examination: Contrast-Enhanced CT **(Figure 1),** whole-body bone scintigraphy **(Figure 2),** and fluorodeoxyglucose PET/CT **(Figure 3)** with FDG showed a lesion in the left upper lung, including the right neck and right ischia.

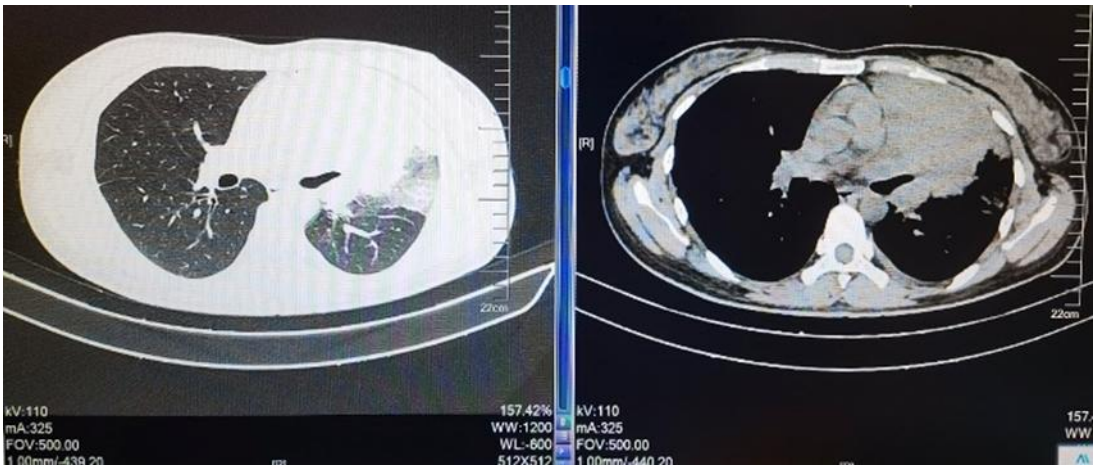

Figure 1: In the upper lobe of the left lung, a little low-density shadow filling can be seen in the lumen of the distal end of the upper lingual bronchus. A mass shadow with a size of about 78*75*96 mm can be seen. The inner density is uneven, the edge is blurred, and the left pleura and oblique fissure are thickened, with left pleural effusion and multiple enlarged lymph nodes in the anterosuperior mediastinum. A ground-glass nodule in the posterior basal segment of the left lower lobe, with a size of about 3*2 mm. The left upper frontal sinus cyst was scanned, and no apparent abnormalities were found in the intracranial and skull.

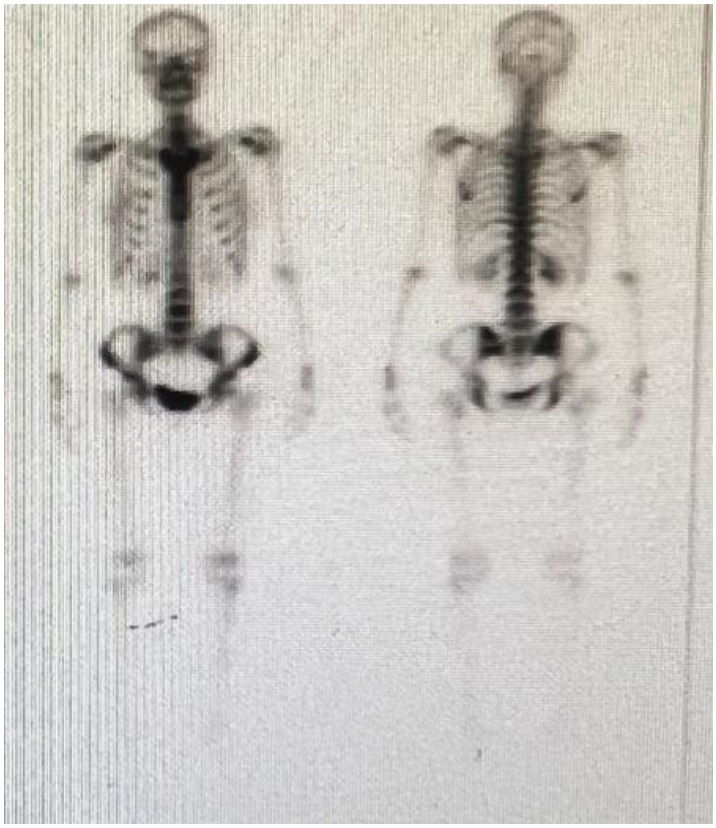

Figure 2: No apparent radioactivity distribution sparse, defect, or abnormal dense shadow foci.

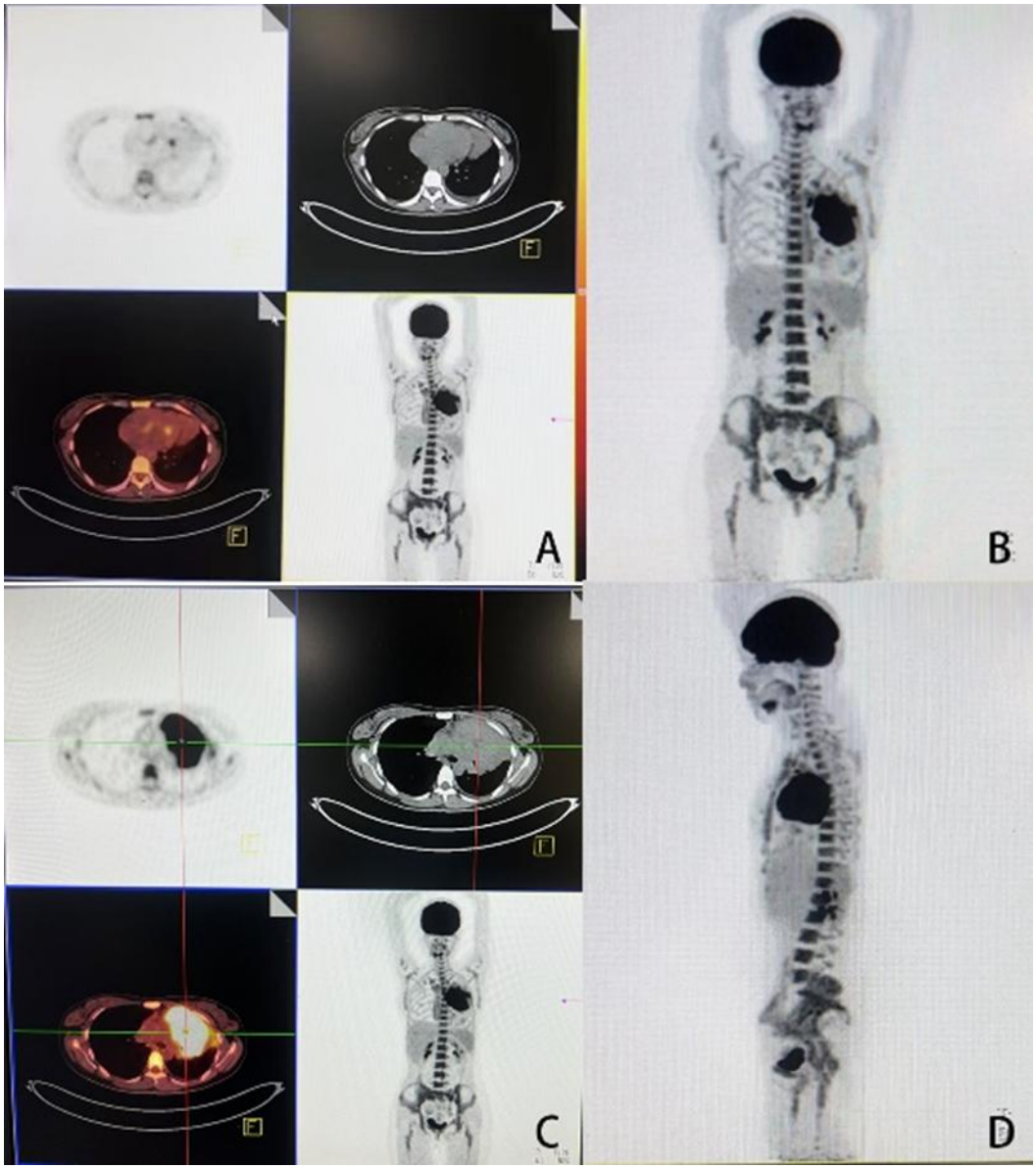

Figure 3: The anterior segment of the left upper lobe and the lingual bronchus are not visualized, and the anterior segment and the lingual segment of the lung tissue show a solid mass shadow; low-density lesions are seen in the central area; still, the possibility of benign lesions is considered high, and the possibility of internal focal tumors cannot be completely ruled out (A); Bilateral posterior mandibular angle, axillary inflammatory lymph nodes, and the lymph nodes adjacent to the aortic arch (B); The inflammatory lesion in the posterior segment of the left upper lobe with left pleural effusion (C); and hemangiomas may appear in the 4th, sixth, and seventh cervical vertebrae and the 3rd, fourth, and fifth thoracic pyramids the; right femoral neck, right ischial tuberosity bone island shadow(D); Abnormally active FDG metabolism in the bone marrow cavity of the whole body (A, D).

Treatment Process: Anti-infection therapy with cefoperazone-sulbactam, levofloxacin, imipenem, moxifloxacin, and vancomycin was administered in stages, but there was no discernible improvement, and the symptoms of cough, sputum, and bloody sputum continued. She was hospitalized in our Thoracic Surgery Department with a lung infection and lung space occupation. Thoracoscopic surgery was used to accomplish a left upper

lobectomy, lymph node sampling, partial pericardial resection, and thoracic adhesion lysis. Additional tests revealed that the lymph node color Doppler ultrasonography, bone marrow aspiration, bone marrow cytology, bone marrow biopsy, and bone marrow flow cytometry were all normal. The Multidisciplinary Team (MDT) recommended combining Brentuximab Vedotin (BV) with R-CHP therapy. FDG-PET is routinely used in the end-of-treatment assessment of PMBL, so the assessment of gray zone lymphoma is also included in the reference. The patient had four standard dose cycles of CD30, Rituximab, ifosfamide, doxorubicin hydrochloride, and prednisone (BV-R-CHP) chemotherapy, followed by a mid-term efficacy evaluation and autologous stem cell collection. PET-CT scan demonstrates assessment of mid-term efficacy, and the patient achieved complete remission **(Figure 4).** Subsequently, BV-R-CHP is continual. Unfortunately, Serious Adverse Events (sAE) made the patient refuse further treatment. Therefore, another four standard dose cycles of R+BV+ PD-1 inhibitor were given. The second curative effect evaluation was performed after the end of treatment and remained CR. And then autologous hematopoietic stem cell transplantation and radiotherapy were performed, and PET-CT evaluation was performed after transplantation, which remained CMR. All in all, after BV-combined therapy, the patient achieved complete remission and has remained in complete remission for two years since she ended the treatment.

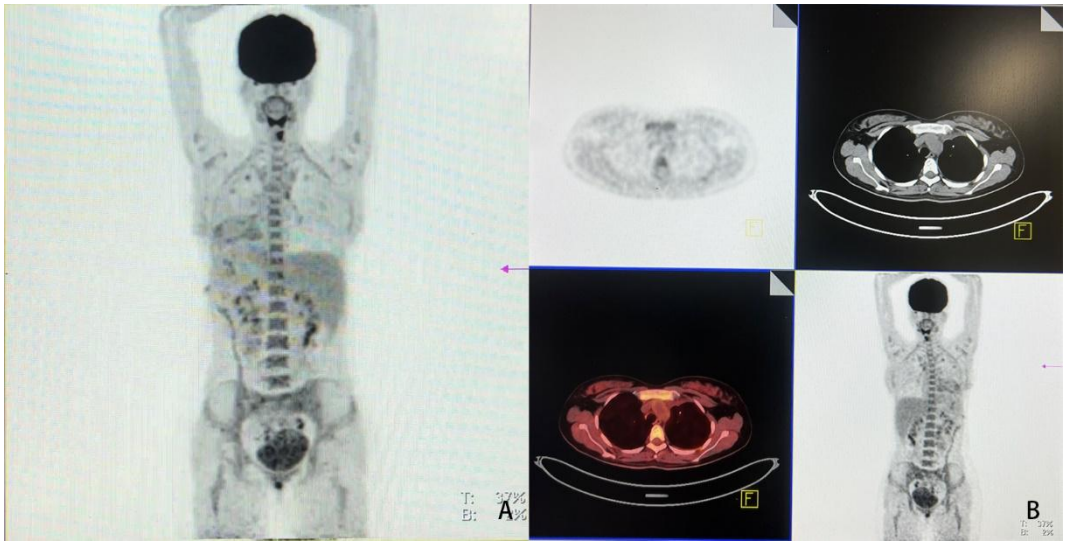

Figure 4: Lymph nodes before the carina were developed, the possibility of inflammatory lesions was considered high (A), and a small amount of effusion in the left chest, no FDG metabolic abnormalities in the left residual lung, and no signs of local tumor infiltration (B).

Discussion

Grey Zone Lymphoma (GZL) was originally included in the 2008 World Health Organization classification as a B-cell lymphoma unclassifiable with the characteristic between Diffuse Large B-Cell Lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL) **[5].** In the latest years, new molecular and genetic features and clinical knowledge have been learned **[9,10].** Clinically, GZL was considered as primary mediastinal localization/ Mediastinal GZL (MGZL) or systemic disease without mediastinal involvement/ with Non-Mediastinal GZL (NMGZL), which have relatively high relapse rates, especially compared with primary mediastinal DLBCL or

cHL [8]. As yet, there are no standard management guidelines for GZL. R-CHOP (Rituximab, cyclophosphamide, doxorubicin, oncovin, prednisolone) or dose-adjusted EPOCH-R (etoposide, prednisolone, oncovin, cyclophosphamide, doxorubicin, Rituximab) was recommended for the frontline treatment of GZL [11,12]. In a prospective study, it showed that PFS appeared significantly longer for patients treated with DA-EPOCH-R (2y-PFS52%) compared with ABVD±R (2y-PFS23%). Regimens of increasing dose intensity are beneficial for GZL [12,13]. And consolidative radiotherapy is also used for localized and/or bulky diseases [14]. Unfortunately, GZL has poor prognosis and higher relapsed/refractory rate, especially for systemic disease without mediastinal involvement. Thus, salvage chemotherapy followed by consolidative autologous HSCT should be considered for those patients with relapsed/refractory GZL [15]. The survive rate improved for relapsed/refractory GZL patients who underwent HSCT, compared with those patients who did not have HSCT (2-y OS 88% vs. 67%). Though, novel biological agents for GZL are limited, new targeted therapeutic drugs have been explored in New or R/R GZL. Brentuximab vedotin, programmed cell death-1inhibitors, etc., were applied for the treatment paradigm of GZL for its biological and pathologic examination [16,17].

Brentuximab Vedotin (BV) is an immunoconjugate consisting of a CD30-directedantibody linked to the anti-microtubule agent auristatin. As a new ADC drug, BV has been extensively explored in CD30-positive B-cell lymphoma, including GZL, because it is an immunogenic target in GZL, which has demonstrated much efficiency using BV, combined with chemotherapy in some studies. In this case, the patient's pathological diagnosis was an unclassified B-cell lymphoma with features similar to diffuse large B-cell lymphoma and classical Hodgkin's lymphoma with CD30 positive on immunohistochemical analysis. It was identified as gray zone lymphoma by the pathologist [7]. We know that the prognosis of NMGZL has inferior outcomes compared with MGZL. Interesting, BV-R-CHP were used for GZL patients, which showed 100% ORR and 86% CR and longer survival [16,18]. However, the best treatment method is still being determined; whether combined immunotherapy makes a good response still needs further exploration. Additionally, gray zone lymphoma, as B-cell lymphoma, has similar clinical, molecular, and genetic features to cHL and PMBL associated with Tumor Microenvironment (TME) that combination therapy with PD1 may be effective [17,19]. The efficiency of PD1 inhibitor in GZL have been identified in case report and Check Mate 436 [20]. With pathological diagnostics and immunohistochemical analysis improvement, BV, PD-1 inhibitor and Rituximab received better results in gray zone lymphoma, especially for those patients with poor prognosis, or relapsed/refractory [6,21,22]. In this case, the patient's characteristics were young age, CD30-positive and large lung mass with lower incidence and poor prognosis in GZL. Thus, BV-R-CHP was used for this patient as a first frontline treatment after MDT discussion, and a satisfactory therapeutic effect was achieved in cycles [1-4]. And the next 4 cycles, we used BV-R-PD1 inhibitor for the intolerant serious adverse event. After that, consolidative radiotherapy and autologous stem cell transplantation were done. Luckily, this patient had achieved CMR after four cycles of BV-R-CHP and remained CMR until now.

Conclusion

GZL was diagnosed based on histopathology and immunophenotyping, and most of this kind of GZL have CD30 positive and PD-L1 positive. Thus, Target therapy may be an effective treatment in poor response and high-risk patients, such as NMGZL. Moreover, the efficiency of target therapy combined with chemotherapy needs further studies to confirm.

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