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Case Report

Keywords: Primary pulmonary lymphoma, COVID-19, EBV + DLBCL

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A case of EBV+ DLBCL diagnosed after COVID-19 infection and literature review

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Abstract

Objective: To describe the clinical characteristics and treatment course of a patient diagnosed with Epstein-Barr virus positive diffuse large B-cell lymphoma (EBV+ DLBCL) after past pulmonary lesions regressed and contracting COVID-19. 

Methods: We retrospectively analyzed the clinical characteristics and treatment course of a patient diagnosed with EBV+ DLBCL, who had previously exhibited pulmonary lesions on PET-CT examination more than 7 years ago, which spontaneously regressed without specific treatment, and subsequently developed COVID-19 infection. Relevant literature was also reviewed.

Results: The patient's PET-CT examination more than 7 years ago suggested pulmonary lesions suspicious of malignancy, but further treatment was not pursued. Subsequent follow-up CT scans revealed gradual regression of the pulmonary lesions. Three months ago, the patient presented with symptoms of fever, chills, and limb weakness, and was diagnosed with EBV+ DLBCL based on cervical lymph node biopsy following COVID-19 pneumonia. After treatment with the Rituximab-mini Cyclophosphamide Doxorubicin Vincristine Prednisone (R-miniCHOP) regimen, the patient's condition improved and was discharged.

Conclusion: Primary pulmonary lymphoma (PPL) may progress to EBV-positive diffuse large B-cell lymphoma after regression, potentially influenced by COVID-19. Diagnosis of PPL remains challenging in clinical practice, and timely pathological tissue biopsy is the most effective method for identification.

Key words: Primary pulmonary lymphoma, COVID-19, EBV+ DLBCL

The patient, a 75-year-old male, presents with complaints of "fever and chills accompanied by weakness in all four limbs for 1 day." He was admitted to the Geriatrics Department of the Affiliated Hospital of North Sichuan Medical College in April 2023.

The patient underwent a PET-CT scan in February 2017 (see Figure 1), which showed the following findings: 1. A mass-like soft tissue density lesion with shallow lobulation around the lesion, measuring 72mm in maximum diameter, was observed in the left hilar region. Increased abnormal uptake of 18F-FDG was noted, with a maximum standardized uptake value (SUVmax) of approximately 9.5; 2. Multiple enlarged lymph nodes were observed in the mediastinum, adjacent to the trachea, along the aortic arch, in the main pulmonary artery window, below the tracheal prominence, and posterior to the pretracheal vein. Abnormal uptake of 18F-FDG was seen in these lesions, with an SUVmax value of around 8.3; No significant abnormalities were detected in other areas. The diagnosis of lung cancer with lymph node metastasis was considered. However, the patient refused further investigations such as pathological biopsy. Subsequently, the patient received
palliative dietary therapy and supportive care, without any anti-tumor treatments such as radiotherapy, chemotherapy, or immunotherapy. Follow-up imaging examinations in November 2019 and October 2021 revealed a gradual regression of the pulmonary lesions (see Figures 2 and 3).

On January 22, 2023, the patient presented with fever, cough, sputum production, and other clinical symptoms. The nucleic acid test for COVID-19 yielded a positive result. Chest CT examination revealed viral pneumonia without signs of lung masses or lymphadenopathy (see Figure 4). After antiviral treatment and symptomatic therapy, the patient's condition improved, and they were discharged on February 3, 2023.
In early April 2023, the patient presented again with unexplained fever, chills, and weakness in the limbs. A follow-up chest CT scan revealed the following findings: 1. Multiple infectious lesions in both lungs. 2. Possible pneumonia nodules in both lungs. 3. Enlarged lymph nodes in the mediastinum and left axilla (refer to Figure 5).

The patient was initially diagnosed with bacterial pneumonia and received antibiotic treatment. However, despite treatment, the fever persisted, and subsequently, lymphadenopathy developed in the neck and groin. Further auxiliary examinations revealed: EB virus DNA 6.03E+4 copies/ml; histopathological examination and immunohistochemistry of the neck lymph node showed lymph node destruction, with tissue cells and small lymphocytes in the background, scattered large atypical cells, and Reed-Sternberg (R-S) cells visible. Immunohistochemistry results indicated: CD3(-), CD5(-), CD20(+), CD79a(+), CD30(+), Bcl-2(+), Mum-1(+), CD10(-), Bcl-6(-), PD-1(-), Ki-67(+, 60%), EBER1/2(+), Pax-5(+), CD15(-), ALK-1(-), LCA(±), P53(+, few cells), supporting the diagnosis of EBV+ DLBCL (Epstein-Barr virus-positive diffuse large B-cell lymphoma) (Figure 6).
At 200x magnification, Figure A shows the R-S cells stained with hematoxylin and eosin from the cervical lymph node biopsy. Figure B shows CD20(+), Figure C shows CD79a(+), Figure D shows Pax-5(+), Figure E shows CD10(-), Figure F shows Mum-1(+), and Figure G shows Bcl-6(-).

In May 23, 2023, a repeat whole-body PET-CT scan revealed: Partial enlargement of lymph nodes in multiple parts of the body with abnormal glucose metabolism; lymphoma involving the left wall of the oropharynx; multiple nodular density increases in both lungs with abnormal glucose metabolism, suggesting possible lymphoma infiltration foci.

Final diagnosis: EBV+ DLBCL (Ann-Arbor stage IV, IPI score 5 high-risk group, NCCN-IPI score 8 high-risk group), concomitant with pulmonary infection. The patient was subsequently treated with R-miniCHOP chemotherapy, leading to gradual improvement in symptoms such as fever and systemic lymphadenopathy.

After reviewing previous reports and relevant literature, this case is discussed and literature reviewed:

Regarding the patient's previous PET-CT suggestive of lung occupation with thoracic lymph node enlargement, the case is now analysed retrospectively from the final diagnosis using a monistic approach, and we speculate that the patient's lung occupation with thoracic lymph node enlargement from 6 years ago may have been Primary Pulmonary Lymphoma (PPL). PPL accounts for <0.5% of primary lung cancers, <1% of lymphomas, and about 3%-4% of all extranodal lymphomas[1]. Mucosa-associated lymphoid tissue lymphoma (MALT) accounts for 60-80% of all cases of PPL and diffuse large B-cell lymphoma (DLBCL) for 10-25% of cases [2]. Patients with PPL usually have no specific respiratory manifestations, such as cough, sputum, chest tightness and chest pain, and some may even have no symptoms at all [3]. Similarly the patient in this case never developed clinical manifestations of lung malignancy such as dyspnoea and coughing up blood after the discovery of lung occupancy. Regarding the prognosis of PPL, it varies depending on the type of pathology, with primary pulmonary MALT lymphoma having a good prognosis, with a 5-year survival rate of 90% and a 10-year survival rate of 70%[4]. Spontaneous regression (as opposed to remission) in this case has been documented in the past, and in the treatment of lung MALT
lymphoma, some researchers have suggested a "watch and wait" strategy for lung MALT lymphomas that do not show signs of progression or dissemination over a long period of time [5]. During treatment for MALT lymphoma, its subsequent recurrence may occur in the lungs, but also in the stomach, salivary glands, and/or lymph nodes [6]. Also in haematological malignancies, there is progression of low-grade tumours to higher-grade tumours, and in PPL low-grade B-cell lymphomas (e.g. MALT) may also transform to pulmonary DLBCL [7]. Therefore, it is speculated that the lung occupation with enlarged thoracic lymph nodes in our patient 6 years ago might be PPL, but there are fewer reports in the literature about the progression of pulmonary MALT lymphoma to DLBCL, and the mechanism of which is not clear for the time being, and it is especially rare that the spontaneous regression of PPL under the influence of neocoronaviruses after the eventual diagnosis of EBV(+) DLBCL, as in the present case considered, is made.

Epstein-Barr virus positive diffuse large B-cell lymphoma, not otherwise specified (EBV+ DLBCL, NOS), is a B-cell disease recognised in the 2016 revision of the World Health Organisation's fourth edition of the classification [8]. It usually expresses the pan-B-cell markers CD19, CD20, CD22, PAX5 and CD79a and has a non-growth centre-like immunophenotype (CD10-, BCL-6/+, IRF4/MUM1+) [9]. EBV(+) DLBCL is a rare subtype of aggressive lymphoma that is poorly responding to conventional chemotherapy, and is currently known for a relatively short period of time, with specific pathogenic principles still unclear. It is known to be strongly associated with EBV infection, which can cause several human malignancies, including Hodgkin's lymphoma, Burkitt's lymphoma, diffuse large B-cell lymphoma, natural killer (NK)/T-cell lymphoma and nasopharyngeal carcinoma [10]. This case differs from conventional EBV(+) DLBCL in that - after the patient's previous lung occupations resolved on their own, she developed several symptoms of lymphoma, such as fever and enlarged lymph nodes, only 3 months after the current infection with the novel coronavirus.

Studies have shown that infection with the novel coronavirus has a profound effect on the immune system, causing alterations in the number and function of different immune cell subpopulations [11]. Meanwhile the immune system continues to be severely affected during recovery from the novel coronavirus [12]. In this case, the patient was finally diagnosed with EBV(+) DLBCL after infection with COVID-19 virus. For that phenomenon, a similar situation was reported in a column in Japan. Two patients developed enlarged lymph nodes after vaccination with the BNT162b2 COVID-19 vaccine and were subsequently diagnosed with diffuse large B-cell lymphoma (DLBCL) [13]. A recent Mendelian randomisation study also suggests that COVID-19 patients with extremely severe respiratory symptoms have an increased risk of developing diffuse large B-cell lymphoma (IVW, OR = 1.765, 95% CI 1.174-2.651, p = 0.006) [14]. Whether there is a direct link between the two, we do not have a clear answer for the time being, but the possible mechanisms between COVID-19 and DLBCL are considered as follows: Abnormal elevation of interleukin 10 (IL-10) serum levels in severe COVID-19 infection [15]. Janus kinase (JAK/STAT) gene expression regulates novel coronavirus-induced complement activation [16]. Also cytokines IL-2, IL-6 and IL-10, as well as epidermal growth factor (EGF) are involved in the strong activation of the JAK/STAT pathway in patients with DLBCL [17]. In addition, the JAK-STAT pathway was shown to be enriched in EBV+ DLBCL in gene expression profiling (GEP), a finding that has been confirmed in cell lines and also by immunohistochemistry [18].
In conclusion, in this case, the overall condition of the patient may have been EBV+ DLBCL under the influence of a novel coronavirus after the regression of PPL; however, we do not know whether there is any correlation between the regression of PPL, the new coronavirus infection, and the final diagnosis of EBV+ DLBCL, and the rationale for the correlation. Whether the mechanism of action may have an impact on the development and transformation of haematological malignancies and their prognosis still deserves further exploration.

Declaration

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Ethics approval and consent to participate: This case has been reviewed and approved by the Affiliated Hospital of North Sichuan Medical College.

Consent for publication: All authors consent to publication.

Data availability: All images and their corresponding test data are sourced from the Affiliated Hospital of North Sichuan Medical College. It should be noted that these data have been approved for publication by the hospital and the patient’s family.

Author contribution: Li Junxiang、Zhang Xiaoqing、Cheng Fangyuan collected the data. Li Junxiang、Liu Juhua wrote the manuscript. Gu Jianwei、Li Junxiang prepared figures. All authors reviewed and approved the final manuscript.

References


