



Case report

A case of resected pulmonary lymphomatoid granulomatosis

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ABSTRACT

Lymphomatoid granulomatosis (LYG) is a rare Epstein-Barr virus-associated B-cell lymphoproliferative disorder and was incorporated into the WHO classification of Tumours of the Lung, Pleura, Thymus and Heart in 2015. LYG is known to be associated with the host's immune function, and can be caused by some immunosuppressive agents, including methotrexate. A woman in her sixties with an 18-year history of methotrexate treatment for rheumatoid arthritis visited our hospital after detection of an abnormal chest shadow on her radiograph. She had been having anemia and a slight fever. Computed tomography (CT) revealed a 2.9-cm sized nodule in her left lung and hilar adenopathy, which suggested a primary lung carcinoma or an inflammatory lesion. We performed a left upper lobectomy with lymph node dissection for the purpose of diagnosis and treatment. Pathologic findings revealed that the tumor was a grade 3 LYG based on the number of EBV-positive B cells. The patient was treated with two chemotherapy regimens including R-CHOP at another hospital, and survived for four years after resection without recurrence in the lung. It is rare to find a case resected LYG, and the clinical or pathological findings of our case are expected to be extremely helpful in studying this disease and improving the understanding of this disease.

1. Introduction

Lymphomatoid granulomatosis (LYG) is a rare lymphoproliferative disorder driven by the Epstein-Barr virus (EBV) and often develops as a methotrexate-associated lymphoproliferative disorder. LYG involves extra-nodal sites including the lungs, skin, central nervous system, liver, and kidneys. When it affects a single lung nodule, it could be difficult to distinguish from other lung nodules, including primary lung carcinoma or other granulomatous lesions in the lung on imaging. We should carefully survey patients' symptoms or prescription history to make an accurate diagnosis of LYG.

2. Case presentation

A woman in her sixties, found out to have anemia, was referred to our hospital. She had been suffering from rheumatoid arthritis for 18 years and was on methotrexate prescribed by her doctor. No source of bleeding was identified by endoscopic examination. On a chest radiograph taken a month after her first visit, an abnormal shadow in her left

lung was noted. She revisited our hospital and was admitted in the department of respiratory medicine for a detailed examination. On admission, she had a slight fever of 37 °C and complained of drenching night sweats. Physical examination revealed the following: body temperature, 36.3 °C (37.6 °C at night); heart rate, 85 beats per minute; blood pressure, 142/96 mmHg; and no rale, was noted. She had never smoked. Laboratory data included: RBC, $4.40 \times 10^6/\mu\text{L}$; hemoglobin, 11.3 g/dL; lactate dehydrogenase (LDH) (reference value), 251 (120–240) IU/L; C-reactive protein, 3.51 g/dL; soluble interleukin-2 (IL-2) receptor (reference value), 1320 (145–516) U/mL. Her chest X-ray and computed tomography (CT) showed a solid 2.9×2.7 -cm sized nodule in the middle of her left upper lobe (Fig. 1). The tumor size increased within a few months. Ipsilateral hilar adenopathy was also seen. We performed bronchoscopy with both exfoliative and lavage cytology, and neither of them indicated malignant findings, lung carcinoma or other malignancies were suggested based on these imaging findings. Although it may not have been malignant, some inflammatory diseases such as mycosis or granuloma could have caused her symptoms. Given the appearance, we made a decision to perform surgery with

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excision on her lung and performed left upper lobectomy with lymph node dissection for the purposes of diagnosis and treatment. The resected specimen was an irregular, solid, white nodule with extensive yellow necrotic areas in the middle of the lobe (Fig. 2). Histopathological examination showed marked obstruction of vessels with extensive fibrosis around vessels. Severe angiocentric and angiodestructive infiltration of lymphocytes including reactive T-cells were also seen. There were variable numbers of larger atypical cells with large nucleoli, similar to Hodgkin cells, and some multi-nucleated giant cells around the fibrosis (Fig. 3). Immunohistochemical findings showed that the Hodgkin-like cells were positive for CD30, and also for LMP1, a marker for EBV. EBV was also confirmed by in situ hybridization (Fig. 4). Other immunohistochemical staining showed that the atypical cells were positive for CD20 and CD79a focally and negative for EML4-ALK fusion protein. The tumor was diagnosed as grade 3 lymphomatoid granulomatosis. Two of the 55 lymph nodes, one in subaortic (#5) and the other in lobar (#12) lymph node, also had the same lesion with extensive necrosis and eosinophilic infiltration. Even after surgery, she had been suffering from a slight fever, loss of appetite, weight loss, and pleural/peritoneal effusion. An increase in the soluble IL-2 receptor level of 1320 U/mL was also seen. She was transferred to the hematology department of another hospital to receive chemotherapy treatment. She was administered two courses of R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) therapy; however, she abandoned it because of a poor response seen on the swollen lymph nodes throughout the body and soluble IL-2 receptor level, and myelosuppression caused by the agents. Alternatively, she received 20 courses of molecular-target therapy with brentuximab vedotin, an antibody-drug targeting CD30-positive Hodgkin lymphoma and systemic anaplastic large cell lymphoma, although it was not approved as a treatment of DLBCL. She has been carefully followed up at the hospital, and no recurrence in the lung has been noticed four years after the resection.

3. Discussion

Methotrexate-associated lymphoproliferative disorder (MTX-LPD) is an iatrogenic immunodeficiency that mainly occurs in patients with RA who are treated with long-term methotrexate therapy [1,2]. MTX-LPD

was initially reported by Ellman in 1991 [3], was increasingly reported as MTX became a common therapy for RA, and has been listed as one of the serious complications in the MTX treatment guidelines in Japan. The LPD incidence ratio of RA patients is two to four fold in the control healthy population irrespective of MTX treatment [4]. MTX-LPD is categorized as other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPD) according to the 2008 and WHO classification [5]. The pathological features of MTX-LPD vary; diffuse large B-cell lymphoma (DLBCL) type is most predominant (35–60%) followed by Hodgkin lymphoma (HL) type (12–25%) [4]. The positive rate for EBV is about 40%, especially high (70%) in HL type [4]. Making a diagnosis of MTX-LPD only by its histological findings is supposed to be extremely difficult considering that there are various histological types of this disease. Unlike other lymphoproliferative disorders, MTX-LPD often involves extra-nodal organs, including the lung, skin, pharynx/tonsil, and soft tissues. Approximately 40–70% of patients with MTX-LPD regress after MTX withdrawal [1], so the first step is the withdrawal of MTX [5]. Meanwhile, relapse/regrowth events (RRE) after regression are seen in some cases of MTX-LPD. Tokuhira et al. reported that MTX-LPD presents three patterns after methotrexate withdrawal to clarify the clinical management of MTX-LPD [5]. A regressive group (R-G) includes patients with LPD regression after immunosuppressive drugs (ISDs) withdrawal without RRE, a relapse/regrowth group (R/R-G) includes patients with LPD regression after ISD withdrawal with RRE, and a persistent group (P-G) includes patients with persistent LPD after ISD withdrawal. Patients in R/R-G and P-G require additional chemotherapy. They also reported that the serum C-reactive protein (CRP), serum soluble IL-2 receptor, and LDH were increased in the P-G group, whereas only CRP and soluble IL-2 receptor were increased in the R/R-G group. In our case, not only swollen lymph nodes but also the level of soluble IL-2 receptor did not regress after MTX withdrawal. This indicates that the patient belongs to the P-G group and requires chemotherapy based on diffuse large B-cell lymphoma (DLBCL), which is the commonest type of MTX-LPD [11].

Lymphomatoid granulomatosis (LYG) is an Epstein-Barr virus-driven lymphoproliferative disorder [6] that has unique histopathologic and clinical features [7]. LYG was initially incorporated into the World Health Organization classification of Tumours of Haematopoietic and Lymphoid Tissues in 2001 [8] and has been categorized as a distinct

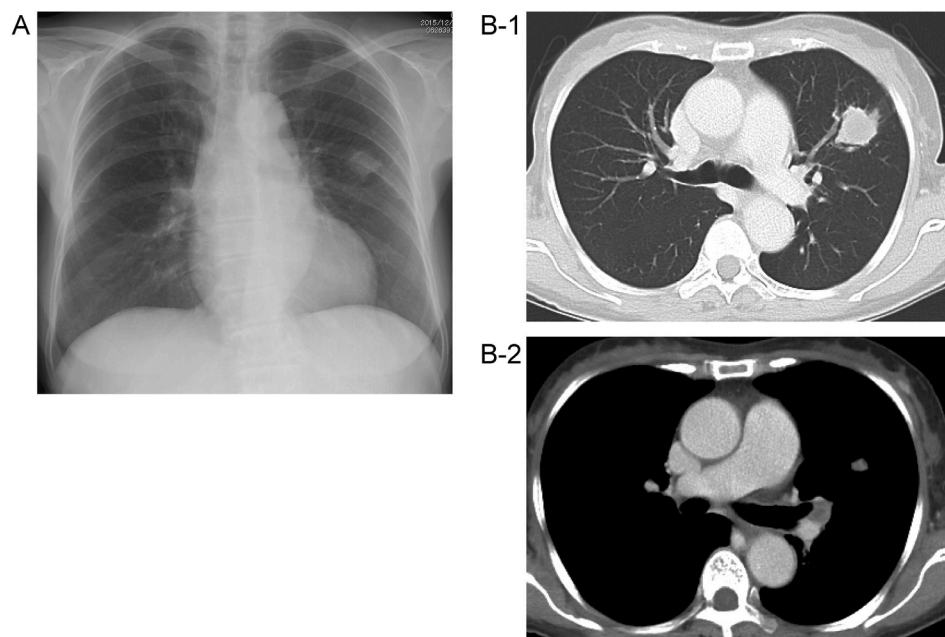


Fig. 1. Chest radiography (A) and CT (B) images revealing a solid mass with the tendency to increase in the left upper lobe. The enlarged hilar lymph node is also seen.

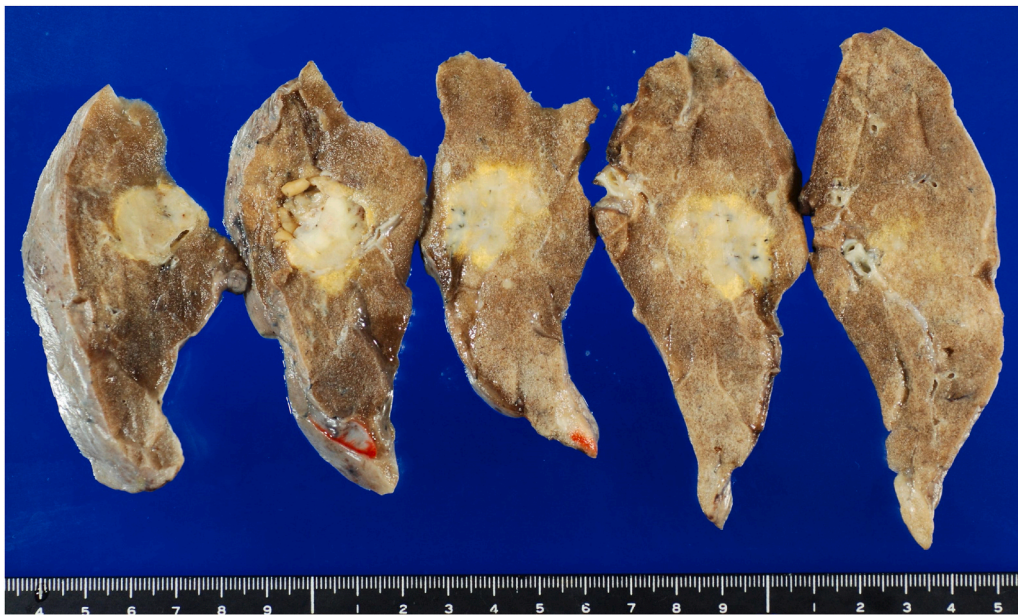


Fig. 2. Partly lobulated white nodule observed in the resected lobe.

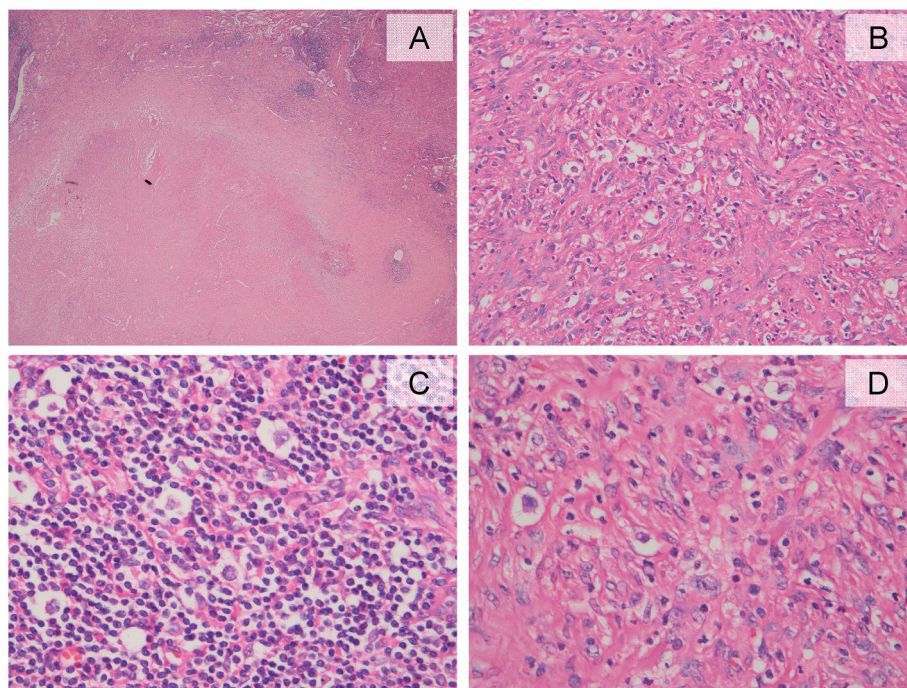


Fig. 3. Histopathological examination revealing central necrosis (A), a proliferation of spindle-shaped cells (B), angiocentric and angiodestructive lymphoid infiltration (C), atypical cells with an irregular nucleus, and multinucleated giant cells (D).

mature B-cell neoplasm in the revised version in 2016 [9]. LYG, characterized by angiocentric and angiodestructive features, typically affects middle-aged adults in the fourth to sixth decades of life, commonly involves the lungs (70%) and involves multiple organs, including the central nervous system (40%), skin (34%), kidney (19%), liver (17%), spleen (10%), lymph nodes (6%), and others (19%) [7,10]. The most common radiographic feature of the lung lesion of LYG is multiple nodules, occurring in approximately 80% of all cases [11,12]. Single lung nodules rarely appear in LYG patients and are used to discriminate other diseases, such as lung cancer, primary pulmonary lymphoma, and other granulomatous lung lesions such as sarcoidosis, tuberculous or non-tuberculous mycobacterial infection, and mycosis.

In our case of MTX-induced LYG, the patient had a history of long-term MTX therapy, and a growing single lung nodule and hilar lymph node were observed on preoperative CT findings. She was initially suspected to have lung cancer. Her clinical findings with slight fever or the history of methotrexate intake could help establish an accurate diagnosis of the disease. The postoperative CT findings showed multiple swollen lymph nodes. Furthermore, pathological findings also showed obvious infiltration of tumor cells in the hilar/mediastinal lymph nodes. These features were also typical for MTX-induced LYG.

The chemotherapeutic regimen for LYG, including MTX-LPG/MTX-DLBCL, has not been standardized as it is a rare disease. Chaves et al. reported that approximately three-quarters of patients with LYG (grade

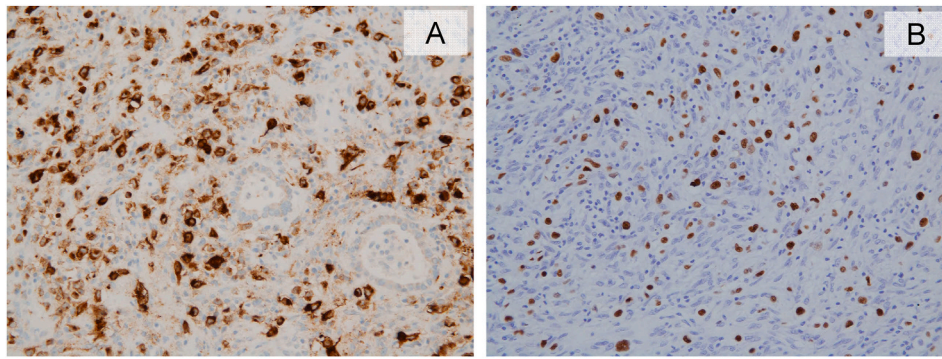


Fig. 4. Atypical cells positive for LMP1, a marker for EBV (A). More than fifty cells are positive for EBV, as assessed by in situ hybridization, per high-power field (B).

3 in 45%) treated with rituximab-based therapies, mainly R-CHOP achieved a response [13]. Another study reported that the overall response rate in patients to combination chemotherapy with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in patients with high-grade LYG was 77% with 41% complete response [2,14]. In our case, the main lung lesion and hilar/mediastinal lymph nodes were removed at the time of surgery; however, serum soluble IL-2 receptor did not respond to R-CHOP therapy. The patient consequently required another chemotherapy regimen and had survived without recurrence.

In conclusion, LYG is not a common disease to thoracic surgeons, but we should consider it as a differential diagnosis in patients with a single lung nodule or multiple lung nodules and a prescription history of immunosuppressive agents, including methotrexate. The clinical and pathological findings of our case are expected to help acquire an easier diagnosis and a deeper understanding of LYG as one of MTX-LPD.

Declaration of competing interest

All authors declare no potential conflict of interest.

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