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# A rare case of pulmonary lymphomatoid granulomatosis complicated with venous thrombosis

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**Abstract.** Lymphomatoid granulomatosis (LG) is Epstein-Barr virus associated and aggressive B cell lymphoproliferative disease. The most common sites of involvement are lungs, skin, kidneys, liver and central nervous system. The clinical presentation of pulmonary LG may mimic infectious diseases, malignancies or vasculitis. While treatment approach of low grade disease is watch and wait, patients with advanced stage require aggressive treatment with chemotherapy. Patients with hematological malignancy as well as solid tumors are at increased risk of venous thromboembolic events (VTE). We reported here in a case of pulmonary LG who was complicated with VTE during treatment with chemo-immunotherapy After 4 cycles of R-CHOP, she achieved complete remission for LG and was followed up without relapse for 2 years. She was anticoagulated with Low-Molecular-Weight Heparin (LMWH) during chemotherapy period, and the thrombus improved over the next several weeks. While on this paper written, patient completed her pregnancy successfully under anticoagulation prophylaxis.

**Key words:** Lymphomatoid granulomatosis, Venous thromboembolic events, Pregnancy

## Introduction

Lymphomatoid granulomatosis (LG) is a rare, Epstein-Barr virus (EBV) associated B cell lymphoproliferative disease (1). The disease mostly located in the lungs however sometimes present at other extra nodal sites. The clinical presentation of LG can mimic infectious diseases, malignancies or vasculitis. Patients with an underlying immunosuppression (e.g., iatrogenic, genetic, acquired) have increased risk of developing LG (2–6). The treatment decision depends on the severity of symptoms, the spread of extrapulmonary involvement, and the histopathological grade of the lesion. While treatment approach of low grade (grade 1 or 2) disease is watch and wait with serial examinations, high grade (grade 3) or symptomatic and advanced patients (especially those with neurologic involvement) require chemotherapy. In general, treatment options for these patients follow those for diffuse large B cell lymphoma (7).

Venous thromboembolic events (VTE) occurs in approximately 10% of patients with cancer and it is triggered by the risk factors such as hospitalization and surgery (8,9). We report here a case of a pulmonary LG who was complicated with VTE during treatment

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with chemo-immunotherapy. Patient provided written informed consent.

## Case presentation

A 30 year-old female was admitted with cough, hemoptysis, night sweats, weight loss, fever and chest pain for 2 months. She had no underlying lung disease and no history of smoking and medication. Her medical history revealed that she was investigated in another center due to suspected tuberculosis diagnosis and it was ruled out 3 weeks ago. On physical examination there were no palpable peripheral lymph nodes and on auscultation breath sounds were diminished over the right lung. On laboratory workup hemogram and biochemical parameters including kidney and liver functions were seen in the normal laboratory range. Symptoms attributed to underlying immunodeficiency were not observed in the patient and normal serum immunoglobulin levels were detected.

As the chest X-Ray revealed a right–sided pleural effusion, a diagnostic thoracentesis and pleural biopsy were performed. The pleural effusion was revealed exudative (table1.) but cytological analysis of the pleural fluid did not aid the diagnosis. However chronic pleuritis was reported as a result of pleural biopsy. Computed tomography (CT) imaging demonstrated 4.5 × 5 cm sized, predominantly in the right upper lung fields, irregular contoured, thick-walled, pleural-based cavitary mass lesion closed to the hilar bronchoalveolar structures. (Figure 1a) There was no mediastinal or hilar lymph node enlargement. A hypermetabolic pleural

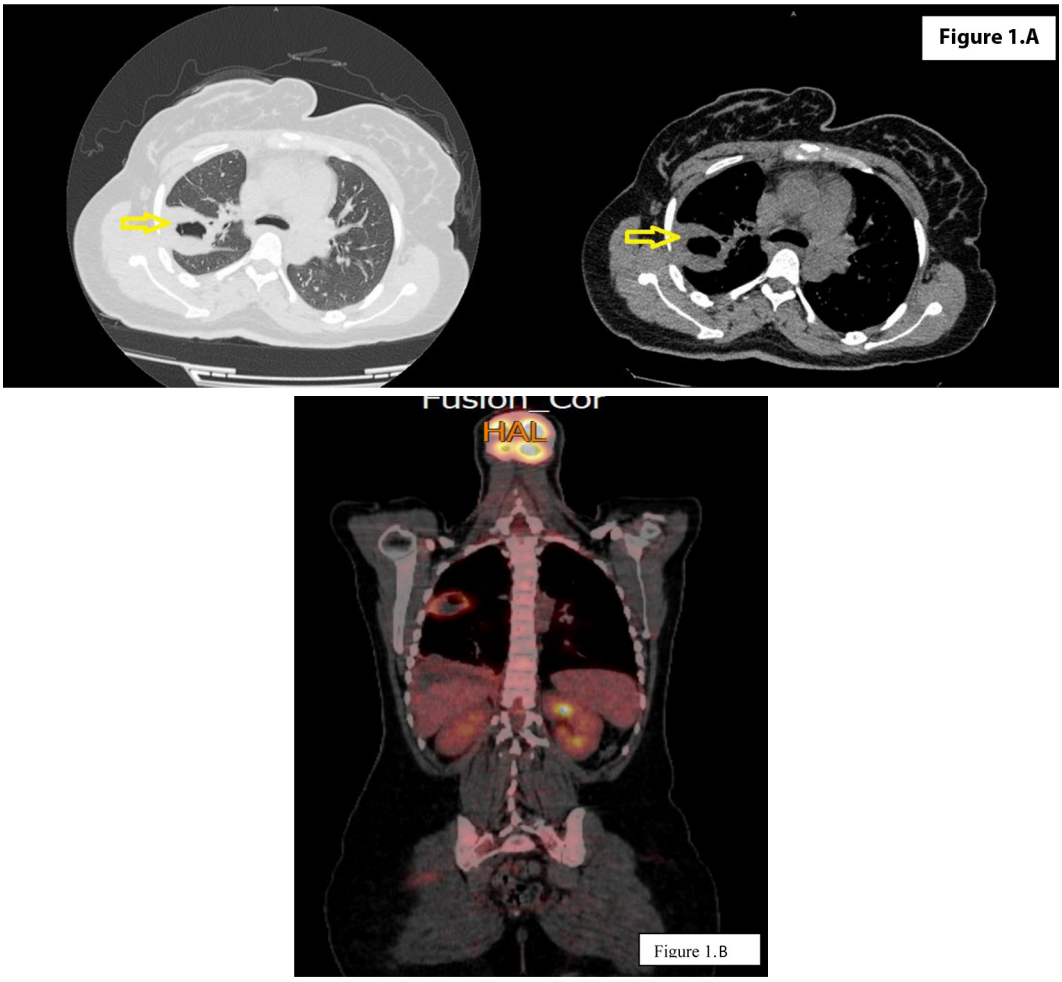


**Figure 1.** (A) Pretreatment CT image of irregular contoured, thick-walled, pleural-based cavitary mass lesion. (B) A hypermetabolic pleural based cavity mass was detected in F18 fluorodeoxyglucose (FDG) positron emission tomography (PET).

based cavity mass was detected in F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) (SUVmax:5.27) and consulted by thoracic surgery department (Figure1b).

Upper lobe wedge resection with right mini-thoracotomy was performed and sample of lesion and lymph nodes near to lesion was investigated by pathology department. (Fig.2). The immunohistochemical study showed granulomatous cells stained positive by anti-CD20, anti-CD30, anti-CD3 and negative with anti-CD15 (Figure 2a,b,Furthermore, in situ hybridization (ISH) showed numerous Epstein-Barr virus (EBV)-encoded small nuclear RNA (EBER) positive cells. Pulmonary LG Grade 2 was diagnosed with normocellular bone marrow (BM) pathology and no other site involvement of disease.

She developed empyema after surgery, therefore tube drainage was inserted. Then R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, every 3 weeks) was started after a delayed period for improvement of empyema. At the third day of chemotherapy, she developed acute VTE in left main femoral vein. She was treated with Low-Molecular-Weight Heparin (LMWH) and investigated for

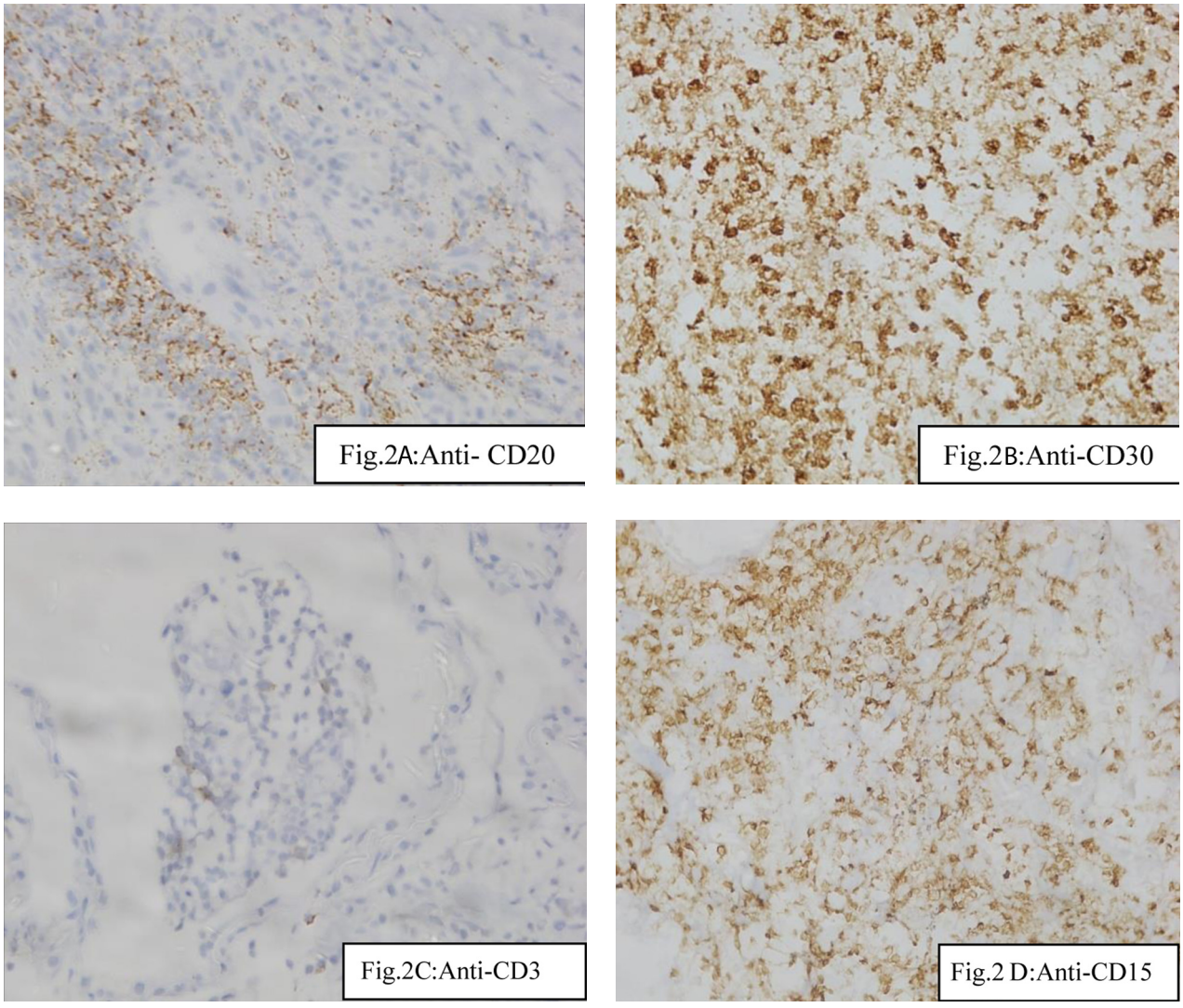


**Figure 2 (A), (B), (C), (D).** The immunohistochemical study showed granulomatous cells stained positive by anti-CD20, anti-CD30, anti-CD3 and negative with anti-CD15, resp.

the etiology for VTE. No genetic risk factor was defined, therefore acquired risk factors particularly malignancy history was considered as etiology of VTE. After 4 cycles of R-CHOP, she achieved complete remission and was followed up without relapse for 2 years. She was anticoagulated with Low-Molecular-Weight Heparin (LMWH) during chemotherapy period, and the thrombus improved over the next several weeks. At the end of second year outpatient follow up, when she declared an unexpected pregnancy, anticoagulation prophylaxis was suggested with enoxaparin 40 mg subcutaneously every 24 hours during ante-partum and post partum periods. While on this paper written, patient completed her pregnancy successfully without any venous complication.

## Discussion

LG is a rare lymphoproliferative disease that is associated with EBV infection more commonly diagnosed in patients with immunodeficiency. Predisposing factors such as medication, viral infections, organ transplantation and lymphoproliferative disorders or congenital diseases may cause underlying immunodeficiency that increases risk of developing LG. Insufficient host response to EBV infection in immunosuppressive patient, may results to occurring LG rather than clearance of the viral infection. It is more common in men and generally occurs in middle-aged patients and rarely in children. Interestingly, our patient was young, had no history of immunodeficiency and no risk factor for immunosuppression.

Up to 90% of LG patients present pulmonary lesions bilateral with multiple nodules in radiological images. Rarely, it is presented as solitary mass with cavitation and pleural effusion. Current case exhibited a single nodule with central necrosis and cavitation and was diagnosed after PET-CT imaging during investigating of tuberculosis. As noticed in our case, clinical and radiological features may cause misdiagnoses, delay in diagnosis and treatment.

Due to rare presentation, there is no standard treatment in LG cases. For low grade patients treating the cause of immune dysfunction and follow up with serial examinations is suggested. Severe disease and high grade cases are required treatment with corticosteroids, interferon and chemotherapeutics such as CHOP or COP regimens with the combination of anti-CD20 monoclonal antibody. Furthermore, the autologous stem cell transplantation may be a successful treatment choice when failure of combination chemotherapy. Current case was presented by systemic symptoms with weight loss, fever and night sweats besides severe pulmonary symptoms. Due to severe symptomatic disease, systemic chemotherapy was required in our patient.

The prognosis of patients with LG is correlated with advanced histopathologic grade (2 or 3) Despite aggressive treatment, high grade disease may be fulminant with median survival of 2 years; the 5-year mortality is 60% to 90% (10). In the literature, recurrence of cases who treated previously and achieved CR has been reported (11).

It is well-known that cancer patients have increased risk of developing VTE compared with normal population. Moreover, cancer patients had a greater incidence during the initial hospitalization and onset of chemotherapy.

In the current case, since no genetic or other risk factors were defined, hypercoagulable state associated with malignancy was considered as etiology of VTE. Cancer tissue is a state of coagulopathy, inflammation and hypoxia, and various substances such as tissue factors and procoagulants are produced by the induction of cancer proliferation genes, which causes thrombus formation. Furthermore, noncardiac thoracic operation history increases incidence of VT ranges from 0.18 to 7.4 percent (12–13). The management of VTE with underlying malignancy is similar to those cases related with other causes. Our patient was treated successfully with LMWH for 4 months. It can be considered that achievement of remission for LG as the predisposing factor also contributed the reveal of VTE. However pregnancy is another hypercoagulable state in our patient. Despite no defined genetic risk factors, we considered using anticoagulant prophylaxis with LMWH for DVT recurrence during ante-partum and post partum periods.

In conclusion, LG is rare hematological malignancy that may provoke VTE as in the setting of other lymphoid malignancies. Clinicians should be aware in complications related with hypercoagulable risk factors during treatment.

**Conflicts of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Informed consent**: Informed consent form of the patient was taken.

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