



# Lymphomatoid Granulomatosis Involving the Lung and Brain in a Child: A Case Report

## 소아 환자의 폐와 뇌에 발생한 림프종모양육아종증: 증례 보고

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Lymphomatoid granulomatosis (LG) is a rare B-cell type angiocentric lymphoproliferative disease that can progress to extranodal lymphoma with high mortality. It most commonly affects the lungs, although extrapulmonary systems, including the brain and skin, can also be involved. LG in pediatric patients has been very rarely reported in the literature with limited imaging features. Herein, we report a pediatric case of LG involving the lung and brain with characteristic imaging findings.

**Index terms** Lymphomatoid Granulomatosis; Magnetic Resonance Imaging; Computed Tomography, X-Ray; Brain; Chest

## INTRODUCTION

Lymphomatoid granulomatosis (LG) is a rare angiocentric lymphoproliferative disease originally described in 1972 by Liebow et al. (1). Initially, LG has been described as a disease mainly affecting the lung, although other organs such as the central nervous system (CNS), skin, kidney, and liver can also be involved. It is now placed in the spectrum of lymphoproliferative diseases (1-4). It mainly occurs in the fourth and fifth decade of life. It tends to occur in immunocompromised patients. It can develop to lymphoma associated with Epstein-Barr virus (EBV) infection. In pediatric population, less than 60 cases have been reported in the English literature with very limited imaging findings to

Received October 30, 2019

Revised February 17, 2020

Accepted May 2, 2020

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the best of our knowledge. Due to its rarity in children, diagnosis of LG is often a challenge to clinicians and radiologists. Herein, we describe clinical and radiologic findings of LG involving lung and brain in a 30-month-old girl who presented with seizure and dyspnea.

## CASE REPORT

A 30-month-old girl who presented with acute onset seizure following fever and cough over one week was admitted to the first institution. She was born as full-term without perinatal problem. She had been healthy except one episode of pneumonia during the neonatal period.

The seizure was generalized tonic-clonic type with duration of 10 min. After seizure, she developed loss of consciousness and severe dyspnea with desaturation.

On physical examination, there were coarse lung sounds and hepatomegaly. There was no abnormal skin lesion. Peripheral blood examination revealed elevated white blood cell count (31380/ $\mu$ L), erythrocyte sedimentation rate (74 mm/hr), and C-reactive protein (7.8 mg/dL). In cerebrospinal fluid study, elevated protein (34.5 mg/dL) and lymphocyte dominancy were present without atypical cell. Serum and sputum examinations for virus and bacteria were all negative except for positive antibody test of EBV.

The initial chest radiograph showed bilateral extensive consolidation of central lung fields with multiple nodules (Fig. 1A). With clinical impression of aspiration pneumonia and meningitis, empirical antibiotics were applied with tracheal intubation. However, there was no clinical improvement and, on the follow-up chest radiograph, pneumonic consolidation did not change either. Without clinical and radiographic improvement, further imaging studies were performed.

Contrast-enhanced chest CT (Fig. 1B) demonstrated extensive variable sized masses and nodules scattered in both lungs as well as consolidative lesions that showed internal lower attenuated areas suspecting necrotic change. Mediastinal and hilar lymphadenopathy was also noted with pleural effusion. In addition, hepatosplenomegaly was present with multiple lymph node enlargements in the covered upper abdomen. Brain MRI after gadolinium injection demonstrated disseminated numerous punctate enhancing foci in the deep gray and white matter of the hemispheres and brainstem. Several homogenously enhancing larger parenchymal nodules were also noted in right frontal and temporal lobes (Fig. 1C). These enhancing brain lesions showed perilesional ill-defined high signal intensity areas on T2-weighted and fluid-attenuated inversion recovery image.

Radiologic differential diagnosis of the intrathoracic lesions included infectious condition including fungus, tuberculosis and malignant tumors such as lymphoma. For the brain lesions, differential included infection, vasculitis and tumor seeding.

Lung biopsy of the left lower lobe mass was performed by video-assisted thoracoscopic surgery. On immunohistochemistry study, CD20 positive cells were present and on in situ hybridization, EBV positive atypical B-cells formed small sheets suggesting grade 3 LG (Fig. 1D).

After the diagnosis, she was transferred to our institution. Staging work up was done. The fluorine-18-fluorodeoxyglucose ( $^{18}$ F-FDG) PET/CT showed increased FDG uptake of the multiple pulmonary lesions (maximum standardized uptake value; SUVmax 10), enlarged lymph nodes at cervical, mediastinal/axillary, abdomino-pelvic cavity and spleen (Fig. 1E). Right

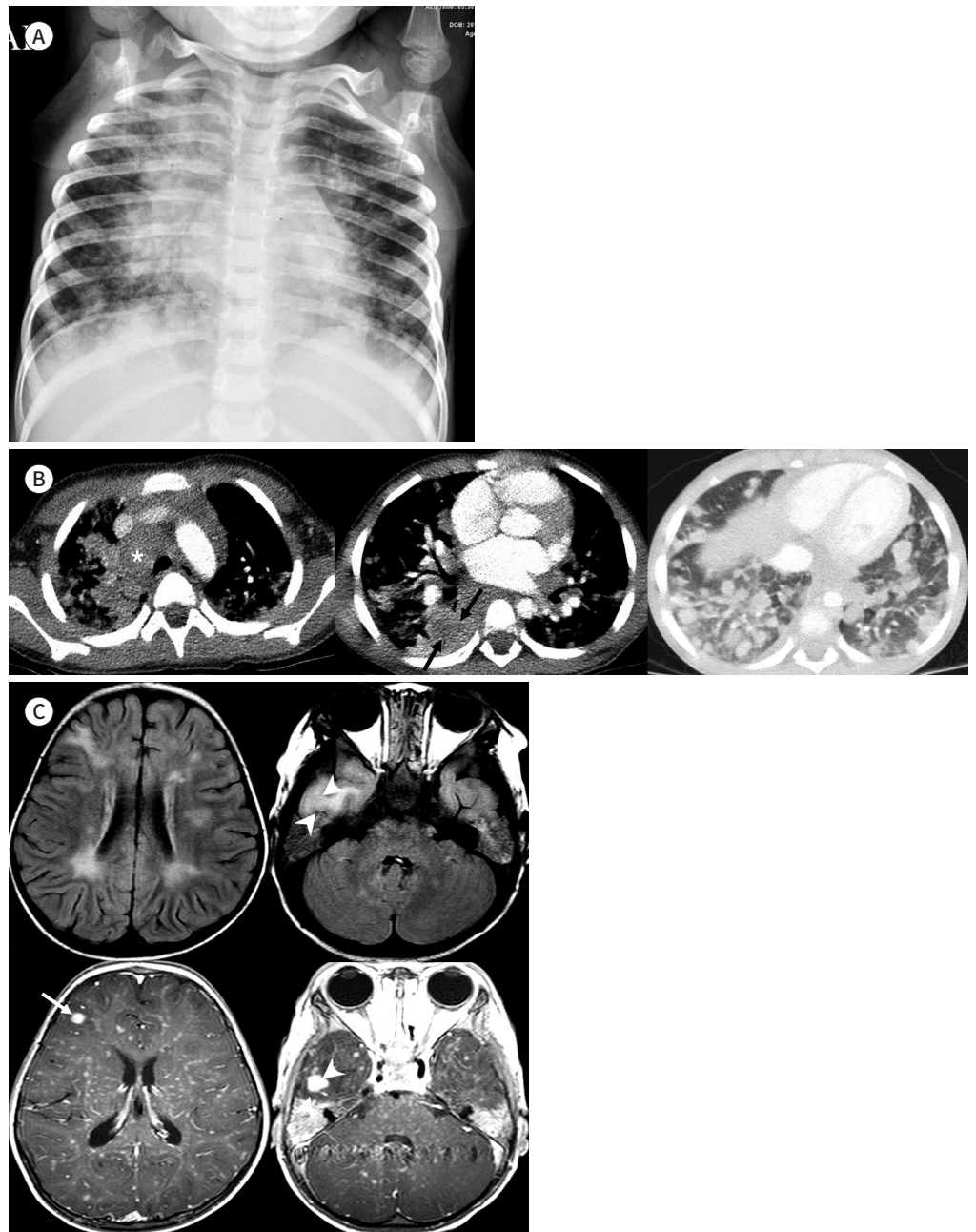
**Fig. 1.** A 30-month-old girl with grade 3 lymphomatoid granulomatosis involving chest and brain.

**A.** Chest anteroposterior radiograph showing extensive peribronchovascular, increased opacities, and multiple nodules in both lungs.

**B.** Postcontrast chest CT axial scans in the mediastinal window (left, middle image) and lung window (right image) settings showing bilateral multiple pulmonary nodules/masses and consolidative right lung lesions with an internal low attenuated area (black arrows on middle image). Mediastinal and hilar lymphadenopathy can be seen (asterisk on left image) with a small amount of right pleural effusion.

**C.** FLAIR axial images of the cerebral hemisphere showing multifocal ill-defined high signal lesions in the white matter (left upper, right upper image). Post-contrast T1-weighted image showing numerous punctate enhancing foci and a nodular enhancing lesion in the right frontal lobe (arrow) (left lower image). At the temporal convexity level, a lesion of isosignal intensity on FLAIR (arrowheads) can be seen (right upper image). Enhancement with perilesional edema can be seen (arrowheads) (right upper, right lower image). There are also multiple punctate enhancing foci in the cerebellar hemispheres (right lower image).

FLAIR = fluid-attenuated inversion recovery



temporal lobe lesion also showed increased uptake (SUVmax 4.5). Bone marrow involvement was identified on biopsy. Finally stage IV disease of lymphoma was confirmed.

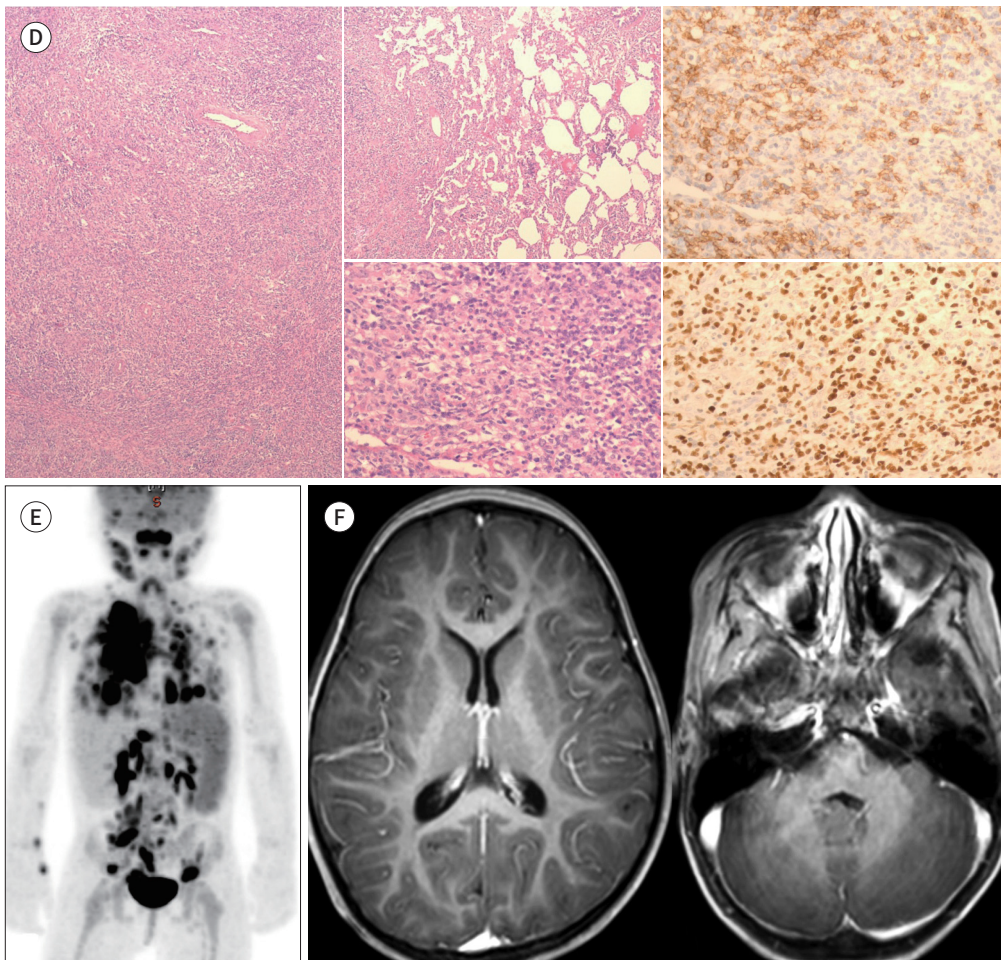
High dose chemotherapy based on treatment protocol of pediatric B-cell lymphoma was performed. Initially, there was good response to the chemotherapy with decrease in size of all brain lesions on follow-up MR imaging (Fig. 1F). However, follow up MRI after eight month of initial diagnosis showed newly appeared adenoid enlargement and increase in size of previous brain lesions. On adenoid biopsy, recurrence of lymphoma was confirmed. Subsequently, induction chemotherapy and peripheral blood stem cell transplantation were done. Afterward, the patient suffered transplantation related complication and died 18 months after the initial diagnosis.

**Fig. 1.** A 30-month-old girl with grade 3 lymphomatoid granulomatosis involving chest and brain.

**D.** Pathology of the lung biopsy specimen. Hematoxylin and eosin staining ( $\times 10$ ,  $\times 40$ , and  $\times 400$ ; left, middle image) showing diffuse infiltration of high grade large atypical lymphocytes admixed with small lymphocytes, plasma cells, and histiocytes. Neoplastic cells are positive for B-cell marker CD20 (immunostaining for CD20; right upper image) and Epstein-Barr virus (Epstein-Barr encoded RNA in situ hybridization) (right lower image).

**E.** PET/CT showing increased fluoro-deoxyglucose uptake of the multiple pulmonary lesions, and enlarged lymph nodes in the cervical, mediastinal/axillary, abdominopelvic cavity, and spleen.

**F.** On follow up MRI, contrast-enhanced T1-weighted image 6 months after the initial diagnosis, the enhancing punctate lesions and mass have resolved.



## DISCUSSION

LG is currently regarded as a part of a spectrum of lymphoma (1) which affects multi-organ. Pulmonary involvement is the most common. The skin is the second most commonly involved organ followed by liver, lymph node, kidney, and spleen (2, 5). Its common clinical presentations include cough, fever, dyspnea, and weight loss (4). Symptoms of pediatric patients are various and they differ from those reported in adults (5). A previous systemic review of LG in 49 pediatric patients by Tacke et al. (2) demonstrated relatively higher incidence of neurological symptoms and more common lymphadenopathy than in adults.

Histopathologic grading is important in prognosis and treatment of patients with LG. LG can be classified into three grades based on the number of neoplastic EBV-positive B-cells and the extent of cellular atypia (3, 6). Grade 1 lesions have polymorphous angiocentric infiltrate composed of small lymphocytes without cellular atypia and infrequent EBV-positive cells. There is no necrosis in grade 1 lesions. Grade 2 lesions have increased numbers of large EBV-positive B-cells with some necrosis. Grade 3 lesions are consisted of abundant atypical EBV-positive cells with extensive necrosis as seen in the specimen of the pulmonary mass in our case. In histopathological exams, EBV is frequently detected in LG. More recent studies using immunophenotyping and EBV RNA *in situ* hybridization have suggested that LG is an EBV-positive B-cell lymphoproliferative disorder with a large number of reactive T cell infiltrates. It tends to occur in immunocompromised patients who are unable to regulate EBV-infected B-cells that accumulate in affected tissues (6). There was no obvious evidence of compromised immunity in our case.

The most commonly reported imaging findings of pulmonary LG on CT are multiple lung nodules or masses frequently found in the lower lung zone (3, 7). These lung lesions are distributed along the bronchovascular bundle, interlobular septa, or subpleural region, reflecting the expected nature of lymphoproliferative disorders (3, 7). The pulmonary lesions are reported to be relatively small, with most of them being less than 1 cm in diameter (7), although larger lesions can commonly present in central low density or cavitation due to central necrosis (3, 7) as seen in our case. According to a few previous cases reports, ground-glass halo sign, reversed halo sign, and coarse linear opacities are reported as less common findings (3, 5, 7). Differential diagnosis of LG includes vasculitis (such as granulomatosis with polyangiitis), other pulmonary lymphoproliferative disease (such as follicular bronchiolitis and lymphoid interstitial pneumonia) and pulmonary metastases (3, 4).

In terms of CNS involvement, the most common MR feature is multifocal T2-hyperintense white matter and gray matter lesions with enhancement (8). Tateishi et al. (8) had reported that multiple punctate and linear enhancements that reside along the perivascular space suggest LG. These findings reflect perivascular and vascular wall infiltration by pleomorphic and lymphoid cells shown in biopsy specimens of the brain (2, 8). Similar to previously reported findings, our case also revealed multifocal white matter lesions hyperintense on T2-weighted image and disseminated punctate enhancing lesions in the white and deep gray matter throughout the cerebral and cerebellar hemisphere and brainstem. There were several larger homogeneously enhancing nodules of iso-signal on T2-weighted image with perilesional edema in the subcortical white matter in the right frontal and temporal lobes. These

lesions did not show diffusion restriction. Without histopathologic confirmation of each brain lesion, we are not sure whether the size of the enhancing lesion is correlated with histopathologic grade of LG. Tateishi et al. (8) have suggested that nodular or mass-like enhancements could represent granuloma formation while punctate and linear enhancements represent abnormal perivascular filtrates and the affected vessel wall regardless of the grade of LG. In the literature, data regarding the correlation of imaging feature and histopathologic grade of LG are scarce. They remain to be elucidated in the future.

A wide spectrum of CT and MR appearances have been reported in cases of CNS LG including unifocal or multifocal white matter and/or gray matter lesions with variable enhancement, simulating a wide variety of diseases such as acute disseminated encephalomyelitis, multiple sclerosis, vasculitis, lymphoma and high grade glioma, metastasis, neurosarcooidosis, leptomeningeal carcinomatosis, and infections, especially tuberculosis in cases with associated pulmonary involvement (8). With relatively high incidence of CNS involvement, a brain MRI evaluation is recommended in children suspected of or diagnosed with LG, even in patients without neurologic symptom.

The prognosis of LG is relatively poor. The mortality rate is about 60–90% during 5 years and a median survival time is about 14 months (5). The optimal management of patients with LG has recently evolved, although there is no standard treatment has been established. There were several spontaneously regressed LG cases of low grade lesions and in patients who are taking immunosuppressive agents such as methotrexate or tumor-necrosis factor inhibitors (5). There was a case report of spontaneous regression of low grade LG in pediatric patient presented as cerebellar mass (9). However, according to a previous report, in high grade LG progressed lymphoma cases it is more aggressive and also has an inferior outcome compared to EBV negative lymphoma (10). In general, patients with low-grade lesions may not need treatment or can be managed with steroids and/or correction of immunosuppression while aggressive chemotherapy should be prompted for higher grade lesions as in our case. The use of chemotherapy has been effective as initial therapy. Recently, rituximab, a monoclonal antibody targeting surface molecules of B-cell, has been promising for treatment of LG (5).

In conclusion, we presented a pediatric case of LG progression to diffuse large B-cell lymphoma involving brain and lung with imaging features. Although LG is very rare in children, a high index of suspicion and awareness of imaging features may allow early diagnosis with timely institution of appropriate therapy.

### Author Contributions

Conceptualization, Y.S.; data curation, H.S.M., C.E.Y., J.B.; investigation, Y.S., H.S.M., J.B., C.E.Y.; methodology, Y.S.; project administration, Y.S.; supervision, Y.S.; writing—original draft, H.S.M.; and writing—review & editing, K.J.H., J.T.Y., O.S.L.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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## 소아 환자의 폐와 뇌에 발생한 림프종모양육아종증: 증례 보고

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림프종모양육아종증은 드문 B 세포형 림프세포증식병으로 추후 림프종으로 발전할 수 있는 높은 치사율을 가진 질병이다. 이는 주로 폐를 침범하며, 흔하진 않지만 뇌, 피부에도 발병할 수 있다. 소아 환자에서 림프종모양육아종증은 매우 드물게 보고된 질병으로 영상의학적 소견의 보고 또한 매우 적다. 저자들은 소아 환자에서 폐와 뇌에서 발병한 림프종모양육아종증 증례와 이의 특징적 영상의학적 소견에 대해 보고하고자 한다.

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