Lymphomatoid Granulomatosis with CNS Involvement can Lead to Spontaneous Remission: Case Study

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Lymphomatoid granulomatosis (LYG) is a rare extranodal angio-centric and angiodestructive multisystem lymphoproliferative disorder. It was first described by Liebow et al. [1]. LYG involves primarily the lungs, but sometimes the skin, nervous system, kidney, and liver are also affected. There are no characteristic clinical manifestations, laboratory examination, or imaging. It comprises abundant admixed reactive T cells with varying numbers of atypical clonal Epstein–Barr virus (EBV)-infected B cells in a polymorphous inflammatory background [2–4]. Few reports on the spontaneous remission of LYG have been published. Here, we describe LYG involving the central nervous system (CNS) and lungs. The patient underwent successful recovery without treatment.

A 24-year-old immunocompetent woman was referred to our hospital complaining of repeated gait disturbance for 18 months. The walk was unsteady walk and accompanied by dizziness and tinnitus without apparent cause. She could not walk in a straight line and fell down readily. Sometimes the manifestations could remit after rest, but the symptoms would reappear if she became tired. She denied having nausea, vomiting, cough, chest pain, or dyspnea.

Neurological examination revealed bilateral positive Babinski reflexes and a slightly ataxic gait. Other physical examinations were unremarkable. General laboratory examinations were normal except that the serum immunoglobulin (Ig) G was 18.34 g/L (reference range, 7–16.6 g/L) and cerebrospinal fluid IgG was 107.00 mg/L (reference range, 10–40 mg/L).

Magnetic resonance imaging (MRI) of the brain demonstrated multiple spotty lesions in the cerebrum, cerebellum, and brainstem, with long T1 and T2 signals and marked gadolinium

enhancement (Figure 1A). Computed tomography (CT) of the chest showed multiple tiny nodules in both lungs (Figure 1B).

Video-assisted thoracoscopic biopsy of the right lung was carried out. Pathological findings revealed angiocentric and granulomatous necrosis with few EBV-EBER-positive cells. Immunohistochemical staining for CD3 and CD20 showed numerous T cells and a few B cells, scattered and in small aggregates (Figure 2), confirming the diagnosis of grade-1 LYG.

Her symptoms were mild, so we did not initiate treatment other than follow-up. We requested her to carry out more exercise and have plenty of rest. One month after discharge from hospital, she could attempt to walk in a straight line without assistance. Three months later, her symptoms had disappeared completely. MRI (Figure 1C) and radiographs were repeated: No lesions in the brain or lungs were noted. Our patient was in complete remission by 1 year with no recurrence of original presentations.

LYG is thought to be associated with EBV infection, but the exact etiology is not known. LYG is also suspected to have a complex relationship with immune function [2] and tends to affect immunodeficient subjects [3]. Fever and persistent cough are the most common presenting symptoms of LYG, whereas multiple (usually bilateral) chest infiltrates or nodules are present in most individuals [4]. LYG can affect any site in the CNS, and symptoms (headache, psychiatric change, epilepsy, hemiplegia, ataxia, and hemorrhage) are dependent on which site is involved. However, the diagnosis in a patient without concomitant pulmonary symptoms may be difficult [3].

Our patient presented with slight ataxia with no symptoms in the lungs even though imaging revealed striking numerous granulomatous lesions in the brain and lungs. The inconsistency

Figure 1 Magnetic resonance imaging (MRI) of the head and Computed tomography (CT) of the lung. **(A)** Numerous spotty high-signal lesions are observed in the brainstem and cerebellum on the T2-weighted image. These lesions are enhanced with gadolinium on the T1-weighted image. **(B)** Nodular lesions are observed in both lungs. **(C)** MRI of the head 3 months later when the final diagnosis was made. T2-weighted image and T1-weighted images with gadolinium enhancement do not show abnormalities. Compared with **(A)**, the lesions have disappeared.

Figure 2 Histopathological examination of lung specimen. **(A, B)** Small lymphocytes are admixed with histiocytes. Occasionally, atypical large lymphoid cells infiltrate the regions around the blood vessels with characteristic angiocentric and angiodestructive patterns (hematoxylin and eosin stain, original magnifications **(A)** $\times 200$, **(B)** $\times 400$). **(C)** CD20-positive large cells scattered and in small aggregates are B lymphocytes (immunohistochemistry, original magnification $\times 200$). **(D)** Numerous reactive small lymphocytes stained positive for CD3 in the background (immunohistochemistry, original magnifications $\times 200$).

between symptoms and radiological findings suggested that the disease might be benign and that the basic structures were not totally destroyed. However, these features can also suggest the possibility of LYG, as shown in another case study [5]. We also considered the diagnosis of sarcoidosis, Wegener's granulomatosis, and metastatic tumor before the final diagnosis, but there was no supporting evidence. That is, LYG can be easily misdiagnosed. Our

case demonstrates that, among the various causes leading to the multiple lesions in the brain and lungs, LYG should be kept in mind as an extremely rare but possible diagnosis.

The definitive diagnosis and grading of LYG should be confirmed by pathological findings. The two main diagnostic criteria were proposed by Katzenstein *et al.* [4]. The first criterion is mixed mononuclear cell infiltrates containing large and small

lymphoid cells, often with plasma cells and histiocytes, which replace the lung parenchyma and show vascular infiltration. The second criterion is variable numbers of CD20-positive large B cells, often with atypia, present in a background of CD3-positive small lymphocytes.

Convincing evidence demonstrating an appropriate therapeutic regimen for LYG is lacking. Considering the wide spectrum of differential diagnoses, experimental treatment should start when pathological studies have been completed. For grade-1 or grade-2 LYG, corticosteroids have proved to be transiently effective but have led to a high relapse rate [2]. Research conducted by Dunleavy *et al.* at the US National Cancer Institute demonstrated that interferon $\alpha 2b$ was also effective (initiated at 7.5 million units, up to 40 million units to achieve optimal results, then sustain for 1–2 years) especially for the LYG in the brain [2]. Combined chemotherapy with rituximab has been applied for grade-3 LYG. Radiotherapy has also been used along with chemotherapy for intracranial LYG. Resection is used only for obtaining tissue samples.

The prognosis of LYG is usually poor. In a clinicopathological study of 152 cases, the mortality rates of LYG were high; most deaths occurred within the first 2 years, and the median survival time was only 14 months [6]. The histological grade of LYG is correlated with outcome. Grade-1 LYG is, in general, benign. Grade-3

LYG is considered a subtype of diffuse large B-cell lymphoma (DLBL). LYG with CNS involvement usually infers a poor prognosis [6]. Lucantoni *et al.* reported four cases of primary cerebral LYG and reviewed 18 early reported cases of isolated CNS-LYG. They suggested that primary cerebral LYG appeared to have a better prognosis than systemic LYG with CNS involvement [7].

In our patient, the final diagnosis was grade-1 LYG. Considering that she was immunocompetent, her symptoms were not severe, and there were possible adverse drug reactions, we decided to follow-up instead of drug treatment. She improved 3 months later, and her condition has remained stable for 1 year. This is the first case of spontaneous remission of LYG with CNS involvement in such a short time without treatment. We believe that improved underlying immunity may explain the findings.

In conclusion, our patient's favorable prognosis suggested that low-grade LYG could result in spontaneous remission and that, if the symptoms are minimal, rest and follow-up may be the best treatment. Our data also suggested that systemic LYG with CNS involvement might also have a good prognosis.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Liebow AA, Carrington CR, Friedman PJ. Lymphomatoid granulomatosis. *Hum Pathol* 1972;**3**:457–558.
2. Roschewski M, Wilson WH. Lymphomatoid granulomatosis. *Cancer J* 2012;**18**:469–474.
3. Mizuno T, Takanashi Y, Onodera H, *et al.* A case of lymphomatoid granulomatosis/angiocentric immunoproliferative lesion with long clinical course and diffuse brain involvement. *J Neurol Sci* 2003;**213**: 67–76.
4. Katzenstein AL, Døxtader E, Narendra S. Lymphomatoid granulomatosis: Insights gained over 4 decades. *Am J Surg Pathol* 2010;**34**:e35–e48.
5. Ishiura H, Morikawa M, Hamada M, *et al.* Lymphomatoid granulomatosis involving central nervous system successfully treated with rituximab alone. *Arch Neurol* 2008;**65**:662–665.
6. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: A clinicopathologic study of 152 cases. *Cancer* 1979;**43**:360–373.
7. Lucantoni C, De Bonis P, Doglietto F, *et al.* Primary cerebral lymphomatoid granulomatosis: Report of four cases and literature review. *J Neurooncol* 2009;**94**:235–242.