

[CASE REPORT]

The Spontaneous Regression of Grade 3 Methotrexate-related Lymphomatoid Granulomatosis: A Case Report and Literature Review

Naoto Aiko¹, Akimasa Sekine¹, Shigeaki Umeda², Takuma Katano¹, Goshi Matama¹,
Kohsuke Isomoto¹, Ryota Otoshi¹ and Takashi Ogura¹

Abstract:

Lymphomatoid granulomatosis (LYG) is a rare lung disorder diagnosed by radiological imaging of multiple pulmonary nodules and occasionally induced by methotrexate (MTX) use. To date, the treatment of LYG has not been standardized. We herein report the case of a patient with grade 3 MTX-related LYG who presented a bulky lung mass. Importantly, the disease condition only improved after the discontinuation of MTX and remained stable for more than 1 year. Chest physicians should be aware that LYG can develop as a single lung mass and spontaneously regress, even without aggressive chemotherapy, following the cessation of MTX.

Key words: lymphomatoid granulomatosis, rheumatoid arthritis, methotrexate

(Intern Med 57: 3163-3167, 2018)

(DOI: 10.2169/internalmedicine.0542-17)

Introduction

Lymphomatoid granulomatosis (LYG) is a rare disorder characterized by multiple nodular lesions with lymphocytic invasion of the vascular walls (1-3). The development of LYG is associated with the reactivation of Epstein-Barr (EB) virus under an immunosuppressive state (4, 5). Several previous studies have reported that long-term methotrexate (MTX) use induced an immunosuppressive state in patients with rheumatoid arthritis (RA) that resulted in the development of LYG (6). We report the case of a patient with grade 3 MTX-related LYG with a single bulky lung mass, which improved following the cessation of MTX.

Case Report

A 79-year-old man visited our hospital due to cough which had persisted for 5 months. He was an ex-smoker (20 pack-year; however, he had not smoked since he was 40 years of age) and had hemiplegia due to cerebral infarction.

He also had a 29 year-history of RA, which had been treated with MTX (6 mg/week), prednisolone (2.5 mg/day), and clopidogrel (75 mg/day). A chest X-ray and contrast-enhanced whole body computed tomography (CT) revealed a single cavitary mass surrounded by ground glass attenuation in the left lower lobe, and a small amount of bilateral pleural effusion (Fig. 1a, b) without mediastinal or hilar lymphadenopathy. The patient did not present any B symptoms (10% weight loss, fever, night sweat), and a physical examination showed no abnormalities (including skin rash and abnormal breath sounds). The patient's laboratory data were as follows: white blood cell count (WBC), 8,400/ μ L; neutrophils, 83%; lymphocytes, 6.1%; monocytes, 9.6%; eosinophils, 0.3%; lactate dehydrogenase (LDH), 220 U/L; C-reactive protein (CRP), 9.96 mg/dL; rheumatoid factor, 28 IU/mL; anti-cyclic citrullinated peptide antibody, 227.4 mg/dL. The tumor marker levels [including soluble interleukin (IL)-2 receptor] were within the normal ranges. We administered antibiotics (ampicillin and sulbactam) empirically in consideration of the lung abscess. The CRP level decreased slightly from 9.96 mg/dL to 6.71 mg/dL; however, the chest

¹Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Japan and ²Department of Pathology, Yokohama City University Graduate School of Medicine, Japan

Received: November 20, 2017; Accepted: March 28, 2018; Advance Publication by J-STAGE: June 6, 2018

Correspondence to Dr. Naoto Aiko, na1435john@gmail.com

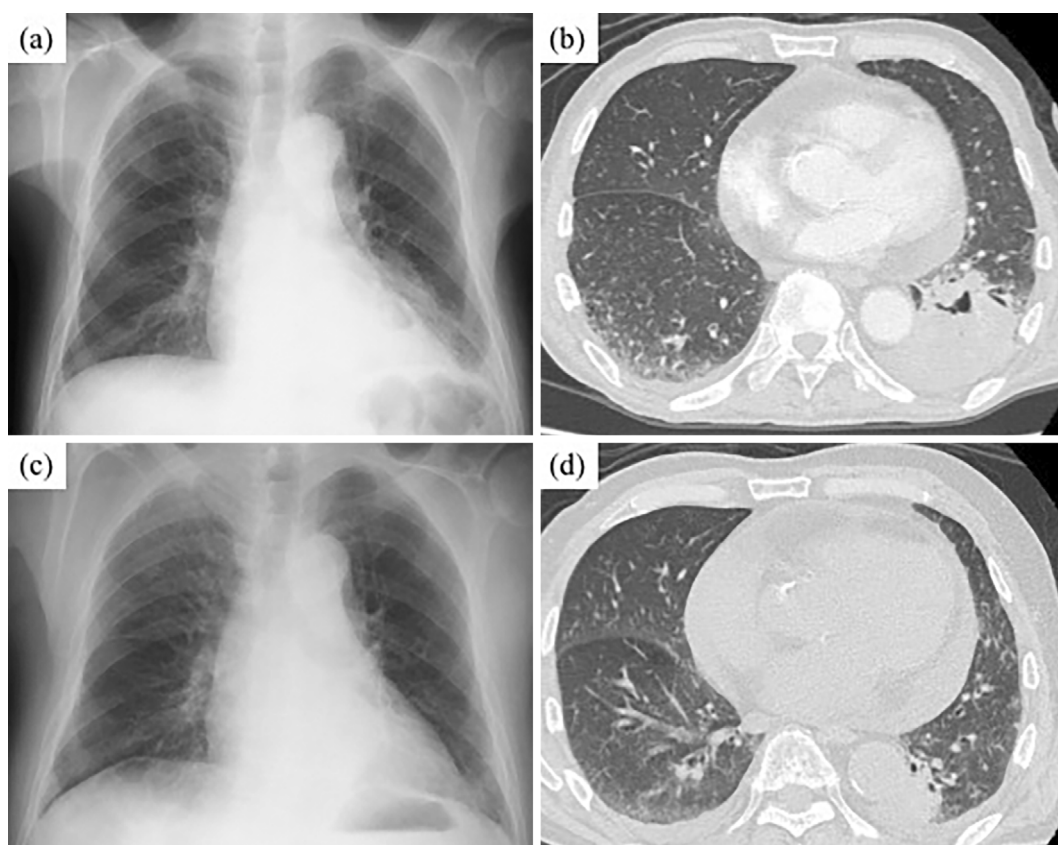


Figure 1. (a) Chest X-ray and (b) chest computed tomography (CT) revealed single pulmonary cavitory mass in the left lower lobe. (c), (d) The pulmonary mass improved and remained stable at 9 months from the day of MTX discontinuation.

X-ray findings showed no improvement. The pathological analysis of a CT-guided pulmonary biopsy specimen demonstrated vascular infiltration of large atypical lymphoid cells surrounded by small lymphocytes and plasma cells (Fig. 2a). The immunohistological findings showed that the large atypical lymphoid cells were positive for CD20 (Fig. 2b) and EBV-encoded small RNA (EBER) (Fig. 2c), whereas the small lymphocytes surrounding the areas of dense infiltration of large atypical lymphoid cells were positive for CD3 (Fig. 2d). There were 70 EBER-positive lymphocytes per high power field. Serum antibody tests were positive for EB virus nuclear IgG (1 : 320) and negative for EB virus capsid IgM, which is consistent with a prior non-acute EBV infection. The EBV capsid IgG ratio and the early antigen-DR component IgG ratio were abnormally high (1:640 and 1:160, respectively). EB virus DNA was found at 2,000 copies/mL. These results confirmed the reactivation of EBV. Based on these findings, the patient was diagnosed with grade 3 LYG. Because his performance status was 3 at the diagnosis of LYG, MTX was discontinued with careful observation. One month later, the symptoms of LYG disappeared and the lung mass apparently shrunk with the improvement of the high CRP level, which remained stable for 15 months (Fig. 1c, d).

Discussion

LYG is a rare, EBV-associated, extranodal B-cell lymphoproliferative disease. The lung is the most common site of involvement (>90%) with or without skin (25-50%), renal (32%), liver (29%), and central nerve (32%) involvement (1). The diagnosis of LYG requires the histological demonstration of angiocentric and angiodestructive lesions consisting of populations of small lymphocytes, plasma cells, histiocytes, and large atypical lymphoid cells. An immunohistological investigation to identify the B-cell subset, and to demonstrate EBV infection by EBER, is helpful in confirming the diagnosis. The severity of LYG is graded as 1 to 3 according to the number of EBER-positive large B cells.

Our report describes the case of a patient with MTX-related LYG who presented with a bulky mass, which shrunk after the cessation of MTX. The results of our case study indicated the following three clinical implications. First, the discontinuation of MTX without aggressive chemotherapy is an important option for MTX-related LYG patients, even those with high-grade LYG. In fact, in our case of grade 3 LYG, the patient's symptoms, bulky lung mass, and high CRP level improved within one month after the cessation of MTX. To date, the treatment of LYG has not

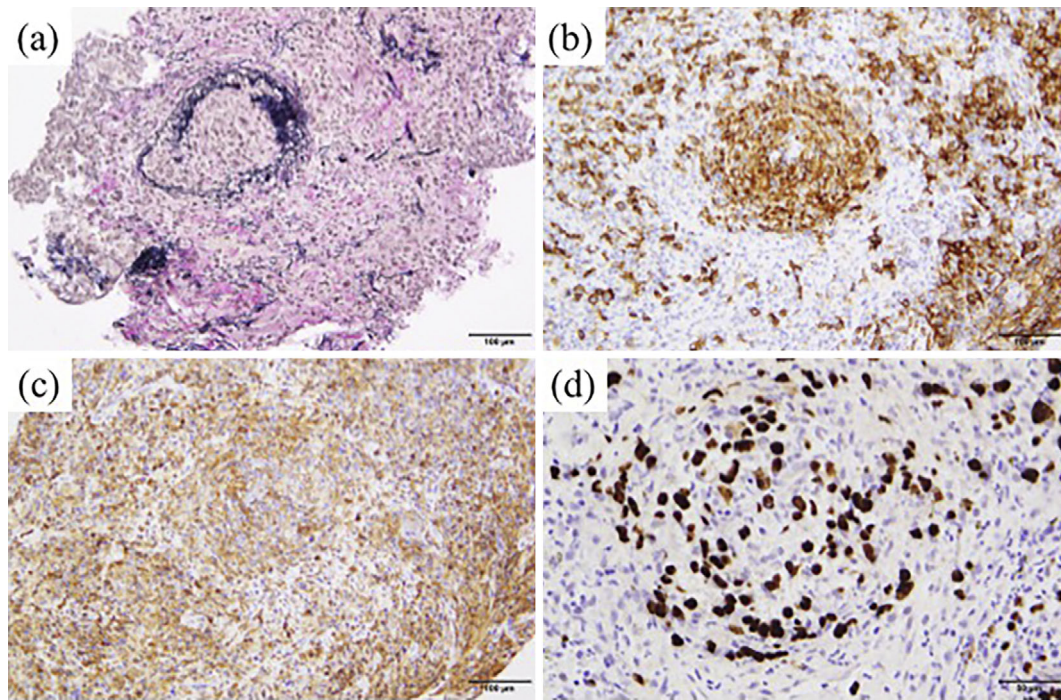


Figure 2. (a) Elastica van Gieson staining image of an infiltrated blood vessel showing predominantly small lymphoid cells with a few large cells. (b) Large lymphoid cells were stained with CD20. (c) Small lymphoid cells around large lymphoid cells were stained with CD3. (d) Epstein-Barr virus encoded RNAs (EBER) were visible following *in situ* hybridization. The number of EBER positive cells was 70 per high power field.

Table. Reports of MTX Related LYG Patient with RA.

Age /Sex	History of RA	Duration of MTX	Grade	Organ involvement	Regression following withdrawal of MTX	Response duration	Ref no.
54 F	24 y	10 y	ND	Pulmonary (multiple), Liver, Spleen	Yes	ND	15
65 F	27 y	17 y	3	Pulmonary (multiple), Skin, Brain	Yes	over 2 y	9
70 F	41 y	5 y	2	Pulmonary (multiple), Kidney, Brain	Yes*	over 6 m	16
71 M	6 y	5 y	1	Pulmonary (multiple), Liver, Spleen, Ileum	Yes	over 8 m	17
73 F	20 y	14 m	2	Pulmonary (multiple), Liver	Yes	over 6 m	18
75 M	12 y	12 y	ND	Pulmonary (multiple)	Yes	over 6 y	19
76 M	18 y	9 y	2	Pulmonary (multiple), Liver	Yes	ND	20
76 F	18 y	18 y	1	Pulmonary (multiple), Liver	Yes	over 20 m	21
76 F	ND	5.5 y	2	Pulmonary (single)	Yes	over 1 y	13
79 F	39 y	18 y	3	Pulmonary (single)	Yes	over 15 m	Our case
60 F	ND	ND	ND	Pulmonary (multiple)	No**	-	22
64 F	ND	10 y	3	Pulmonary (multiple)	No	-	23
70 F	13 y	5 y	2-3	Pulmonary (multiple)	No	-	24
71 M	6 y	29 m	ND	Systemic lymph node (complicated by MTX related interstitial pneumonia)	No	-	25
74 F	28 y	21 m	ND	Skin	No	-	26

* The patient received radiotherapy for brain involvement.

** The patient received chemotherapy immediately after diagnosis.

been standardized. Aggressive combined chemotherapy is often selected for the treatment of high-grade LYG, because grade 3 LYG shows a prognosis that is somewhat similar to that of diffuse large B-cell lymphoma (DLBCL) (1, 7, 8). To the best of our knowledge, there are 14 case reports of MTX-related LYG patients with RA (Table). Nine case reports, including one case of grade 3 LYG (9) described the

improvement of the LYG patient's condition after the withdrawal of MTX, as occurred in our study. A previous study of rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin, and prednisone (R-CHOP) therapy, which is often administered for high-grade LYG and DLBCL patients, reported that grade 3-4 adverse events occurred in 14% of elderly patients (10). Thus, chemotherapy would not always be

the first choice, particularly for elderly LYG patients (such as our patient). These results suggest that the physician should discontinue the administration of MTX first with close observation, then chose R-CHOP therapy if the tumor does not regress.

Second, MTX-related LYG can present as a single mass mimicking lung cancer or abscess. In fact, the patient described in our report developed a bulky mass; thus, lung cancer was suspected before a lung biopsy. Generally, chest radiography typically reveals multiple poorly-defined nodules in the mid and lower lung zones with possible diffuse reticular abnormalities in LYG patients (11, 12). Similarly, patients with MTX-related LYG commonly present multiple masses (Table). Only one case report described a patient who developed grade 2 LYG as a single lung mass (13). These reports suggest that although LYG is a rare disorder, chest physicians should carefully investigate the possibility regardless of the number of pulmonary lesions.

Third, the withdrawal of MTX can be effective—particularly for LYG patients who have undergone long-term MTX treatment. A previous report noted that the incidence of lymph proliferative disorder (LPD) in RA patients was 2.0-5.5 times higher than that in patients without RA, and the interval between RA and the diagnosis of LPD in RA patients treated with MTX was significantly shorter in comparison to patients treated without MTX (14). These results suggest that both RA and MTX can induce the development of LPD. As shown in Table, the duration of MTX treatment was described in 14 of 15 case reports, including our case. Of note, in patients with the spontaneous improvement of LYG after the withdrawal of MTX, the duration of MTX treatment was longer in comparison to those without (median: 10.0 years vs. 3.7 years; Mann-Whitney U test, $p=0.038$). On the other hand, the duration of RA treatment was described in 10 case reports. There was no significant difference in the disease duration of the patients with the spontaneous improvement of LYG after the withdrawal of MTX and those without spontaneous improvement (median: 19.0 years vs. 13.0 years; Mann-Whitney U test, $p=0.55$). Although it is difficult to distinguish whether LYG is induced by RA or MTX in clinical practice, LYG patients who have undergone long-term MTX treatment would be more affected by MTX than by RA. Thus, the withdrawal of MTX could be effective for such patients.

In conclusion, we reported the case of a patient with a bulky mass caused by LYG, which only improved after the cessation of MTX. Chest physicians should be aware that LYG can develop as a single lung mass, and that the discontinuation of MTX without aggressive chemotherapy represents an important treatment choice for LYG. Further studies are necessary to confirm our results.

The authors state that they have no Conflict of Interest (COI).

References

1. Lymphomatoid granulomatosis. In: World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues. Pittaluga S, Wilson WH, Jaffe ES, Eds. IARC Press, Lyon, 2008: 247-249.
2. Cadranet J, Wislez M, Antoine M. Primary pulmonary lymphoma. *Eur Respir J* **20**: 750-762, 2002.
3. Colby TV. Current histological diagnosis of lymphomatoid granulomatosis. *Mod Pathol* **25**: S39-S42, 2012.
4. Katzenstein AL, Peiper SC. Detection of Epstein-Barr virus genomes in lymphomatoid granulomatosis: analysis of 29 cases by the polymerase chain reaction technique. *Mod Pathol* **3**: 435-441, 1990.
5. Guinee DJ, Jaffe E, Koss M, et al. Pulmonary lymphomatoid granulomatosis. Evidence for a proliferation of Epstein-Barr virus infected B-Lymphocytes with a prominent T-cell component and vasculitis. *Am J Surg Pathol* **18**: 753-764, 1994.
6. Hoshida Y, Xu JX, Fujita S, et al. Lymphoproliferative disorders in rheumatoid arthritis: Clinicopathological analysis of 76 cases in relation to methotrexate dedication. *J Rheumatol* **34**: 322-331, 2007.
7. Johnston A, Coyle L, Nevell D. Prolonged remission of refractory lymphomatoid granulomatosis after autologous hemopoietic stem cell transplantation with post-transplantation maintenance interferon. *Leuk Lymphoma* **47**: 323-328, 2006.
8. Jung KH, Sung HJ, Lee JH. A case of pulmonary lymphomatoid granulomatosis successfully treated by combination chemotherapy with rituximab. *Chemotherapy* **55**: 386-390, 2009.
9. Oiwa H, Mihara K, Kan T. Grade 3 lymphomatoid granulomatosis in a patient receiving methotrexate therapy for rheumatoid arthritis. *Intern Med* **53**: 1873-1875, 2014.
10. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* **346**: 235-242, 2002.
11. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. *Cancer Surv* **30**: 233-248, 1997.
12. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. *Cancer* **43**: 360-373, 1979.
13. Ochi N, Yamane H, Yamagishi T. Methotrexate-induced lymphoproliferative disease: Epstein-Barr virus-associated lymphomatoid granulomatosis. *J Clin Oncol* **31**: e348-e350, 2013.
14. Hoshida Y, Xu J, Fujita S, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. *J Rheumatol* **34**: 322-331, 2007.
15. Shimada K, Matsui T, Kawakami M, et al. Methotrexate-related lymphomatoid granulomatosis: a case report of spontaneous regression of methotrexate therapy in rheumatoid arthritis. *Scand J Rheumatol* **36**: 64-67, 2007.
16. Yamakawa T, Kurosawa M, Yonezumi M, et al. Methotrexate-related lymphomatoid granulomatosis successfully treated with discontinuation of methotrexate and radiotherapy to brain. *Rinsho Ketsueki* **55**: 321-326, 2014 (in Japanese, Abstract in English).
17. Kobayashi S, Kikuchi Y, Sato K, et al. Reversible iatrogenic, MTX-associated EBV-driven lymphoproliferation with histopathological features of a lymphomatoid granulomatosis in a patient with rheumatoid arthritis. *Ann Hematol* **92**: 1561-1564, 2013.
18. Ogata T, Shibata S, Matsuoka E, et al. A case of methotrexate-associated lymphomatoid granulomatosis. *Jpn J Lung Cancer* **53**: 234-239, 2013 (in Japanese, Abstract in English).
19. Nakamura T, Maesaki T, Takaoka H, et al. Diversity of nodular lesions in patients with rheumatoid arthritis and methotrexate treatment. *Clin Rheumatol* **28**: 66-74, 2016.
20. Inaba M, Ushijima J, Horata N, et al. Methotrexate related lymphomatoid granulomatosis in a patient with rheumatoid arthritis.

- Nihon Kokyuki Gakkai Zasshi **49**: 597-601, 2011 (in Japanese, Abstract in English).
21. Ishihara S, Izumi H, Nagase D, et al. Multiple lung tumors assumed to be rapidly advancing methotrexate-associated lymphoproliferative disease. *J New Rem & Clin* **64**: 183-189, 2015.
 22. Barakat A, Grover K, Peshin R. Rituximab for pulmonary lymphomatoid granulomatosis which developed as a complication of methotrexate and azathioprine therapy for rheumatoid arthritis. *SpringerPlus* **3**: 751, 2014.
 23. Blanchart K, Paciencia M, Seguin A, et al. Fatal pulmonary lymphomatoid granulomatosis in a patient taking methotrexate for rheumatoid arthritis. *Minerva Anesthesiol* **80**: 119-120, 2014.
 24. Ito S, Shiraishi M, Iwai Y, et al. A case of methotrexate-associated lymphomatoid granulomatosis diagnosed on autopsy. *Jichi Medical University Journal* **38**: 65-69, 2015 (in Japanese, Abstract in English).
 25. Kameda H, Okuyama A, Tamaru J, et al. Lymphomatoid granulomatosis and diffuse alveolar damage associated with methotrexate therapy in a patient with rheumatoid arthritis. *Clin Rheumatol* **26**: 1585-1589, 2007.
 26. Schalk E, Krogel C, Scheinplflug K, et al. Lymphomatoid granulomatosis in a patient with rheumatoid arthritis receiving: successful treatment with the anti-CD20 antibody mabthera. *Onkologie* **32**: 440-441, 2009.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).