CASE REPORT

Mycophenolate Mofetil-induced Diffuse Large B-cell Lymphoma in Which a Solitary Lung Nodule Remitted Spontaneously

Hiroshi Kobe¹, Akihiro Ito¹, Hiroki Hayata², Keisuke Nishimura³, Yasunori Ueda² and Tadashi Ishida¹

Abstract:
A 76-year-old woman with dermatomyositis was being treated with prednisolone, tacrolimus, and mycophenolate mofetil. There was a solitary lung nodule in the right middle lobe on chest computed tomography at a routine follow-up examination. A transbronchial lung biopsy was performed, and the histopathologic findings indicated diffuse large B-cell lymphoma. An immunodeficiency-associated lymphoproliferative disorder was suspected, and mycophenolate mofetil was stopped without adding any other therapy. Nine months later, the pulmonary nodule had disappeared on chest computed tomography.

Key words: mycophenolate mofetil, diffuse large B-cell lymphoma, dermatomyositis, lung nodule

(Intern Med 60: 131-136, 2021)
(DOI: 10.2169/internalmedicine.5027-20)

Introduction
Immunodeficiency-associated lymphoproliferative disorders are classified as a cause of lymphoid neoplasms in the 2016 revision of the World Health Organization classification of lymphoid neoplasms (1). Although many lymphoproliferative disorders have been reported, there have been few reports of mycophenolate mofetil-associated lymphoproliferative disorders related to transplantation but to connective tissue diseases. Furthermore, most mycophenolate mofetil-associated lymphoproliferative disorders were found in the central nervous system and required chemotherapy or radiotherapy. There have been no reports of mycophenolate mofetil-induced lymphoproliferative disorders presenting only with pulmonary lesions.

We herein report the first case of mycophenolate mofetil-induced lymphoproliferative disorder presenting as a solitary lung nodule that remitted spontaneously along with a brief review of the relevant literature.

Case Report
A 76-year-old woman had been diagnosed with anti-PM-Scl75 antibody-positive dermatomyositis (DM) 8 years earlier. Her performance status (Eastern Cooperative Oncology Group) was 1. She had smoked 40 cigarettes a day for 30 years but stopped smoking 15 years earlier. She did not have a family history of lung cancer or malignant lymphoma. She had required treatment with prednisolone, azathioprine, tacrolimus, immunoglobulin, and mycophenolate mofetil (MMF). She was being treated with prednisolone 5 mg/day, tacrolimus 4 mg/day, and MMF 2,500 mg/day at that time. She had taken MMF for four years.

She underwent regular chest computed tomography (CT) follow-up examinations and was referred to the department of respiratory medicine because a solitary 18-mm pulmonary nodule was found in the right middle lobe (Fig. 1). She was asymptomatic at that time. Blood tests showed no remarkable changes (Table 1); the soluble-interleukin-2-receptor (sIL-2R) level was not measured. A transbronchial lung bi-

¹Department of Respiratory Medicine, Ohara Healthcare Foundation, Kurashiki Central Hospital, Japan, ²Department of Hematology/Oncology, Ohara Healthcare Foundation, Kurashiki Central Hospital, Japan and ³Department of Endocrinology and Rheumatology, Ohara Healthcare Foundation, Kurashiki Central Hospital, Japan

Received: April 6, 2020; Accepted: June 29, 2020; Advance Publication by J-STAGE: August 22, 2020
Correspondence to Dr. Hiroshi Kobe, hk16554@kchnet.or.jp
opsys was performed from the right middle lobe. A histopathologic examination showed that the growth of large lymphoid cells was increasing, the formation of nuclear rays was conspicuous, and apoptosis was abundant and accompanied by infiltration of histiocytes. Immunohistochemical staining was positive for CD10, CD20, CD21, bcl-2, bcl-6, and MUM-1, whereas CD3, CD5, CD30, and EB virus encoded small RNA (EBER) were all negative (Fig. 2). Thus, she was diagnosed with diffuse large B-cell lymphoma (DLBCL).

Fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG-PET) (Fig. 3A), a bone marrow biopsy, and upper and lower gastrointestinal endoscopies were performed. There were no other lesions of DLBCL except for the one in the lung. Her Ann Arbor classification was stage IE. An immunodeficiency-associated lymphoproliferative disorder (IA-LPD) was suspected, and MMF was stopped without adding any other therapy. The absolute lymphocyte count (ALC) and lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels remained unchanged between the detection of the lung nodule and two weeks after MMF withdrawal (Table 1). Two months later, the pulmonary nodule in the right middle lobe had decreased to 7 mm (Fig. 3B). Chemotherapy and radiotherapy for DLBCL were postponed.

Nine months later, the lesion disappeared (Fig. 3C). However, her DM had worsened and required increased doses of prednisolone and the initiation of immunoglobulin therapy. After additional treatment, her DM improved.

### Discussion

Ellman et al. (2) reported the first case of methotrexate-associated lymphoproliferative disorder (MTX-LPD) in 1991, and immunosuppressive treatment has been reported to increase the risk of LPD. In the WHO classification, IA-LPD is classified as a kind of malignant lymphoma. It is reportedly caused by not only methotrexate but also fluda-

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**Figure 1.** Chest computed tomography shows an 18-mm solitary pulmonary nodule (arrow) in the right middle lobe.

**Figure 2.** A histopathologic examination showed that the growth of large lymphoid cells was increasing, the formation of nuclear rays was conspicuous, and apoptosis was abundant.

**Table 1.** Laboratory Data of the Present Case.

|                     | The day MMF was started | The day the pulmonary nodule was found | The day MMF was stopped | Two weeks after MMF was stopped |
|---------------------|-------------------------|---------------------------------------|-------------------------|--------------------------------|
| WBC(×10^3/μL)       | 2.800                   | 5.900                                 | 5.400                   | 6.000                          |
| Neutrophils(%)      | 49.6                    | 66.3                                  | 65.5                    | 75.8                           |
| Eosinophils(%)      | 1.1                     | 1.2                                   | 1.7                     | 1.0                            |
| Lymphocytes(%)      | 36.0                    | 24.9                                  | 26.6                    | 18.4                           |
| Monocytes(%)        | 12.6                    | 7.4                                   | 5.6                     | 4.5                            |
| Hemoglobin(g/dL)    | 12.7                    | 9.9                                   | 9.6                     | 9.1                            |
| Platelets(×10^4/μL)| 11.3×10^4               | 21.8×10^4                            | 21.5×10^4               | 17.9×10^4                     |
| Albumin(g/dL)       | 3.0                     | 3.6                                   | 3.6                     | 3.5                            |
| Aspartate aminotransferase(U/L)| 40       | 40                                    | 40                      | 19                             |
| Alanine aminotransferase(U/L)| 42               | 20                                    | 20                      | 20                             |
| Lactate dehydrogenase(U/L)| 253              | 225                                   | 225                     | 243                            |
| Blood urea nitrogen(U/L)| 16           | 25                                    | 22                      | 20                             |
| Creatinine(U/L)     | 0.51                    | 0.67                                  | 0.65                    | 0.66                           |
| Creatinine clearance(ml/min/1.73m^2)| 87.8     | 64.4                                  | 66.5                    | 65.4                           |
| Sodium(mmol/L)      | 136                     | 142                                   | 142                     | 141                            |
| Potassium(mmol/L)   | 4.0                     | 4.3                                   | 4.3                     | 4.8                            |
| Calcium(mg/dL)      | 9.0                     | 9.3                                   | 8.9                     | 8.9                            |
| Creatine(mg/dL)     | 0.11                    | 0.27                                  | 0.07                    | 0.14                           |
| Absolute lymphocyte count(×10^3/μL)| 1,008            | 1,469                                 | 1,436                   | 1,104                          |
| Immunoglobulin G(mg/dL)| -                     | 883                                   | 901                     | 902                            |
| Tacrolimus(trough, ng/mL) | -                  | 6.1                                   | 6.0                     | 4.8                            |

WBC: white blood cell, Neutrophil: neutrophil, Eos: eosinophil, Lymph: lymphocyte, Mono: monocyte, Hb: hemoglobin, PLT: platelet, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CRE: creatinine, eGFR: estimated glomerular filtration rate, Na: sodium, K: potassium, CRP: C-reactive protein, ALC: absolute lymphocyte count
rabin, infliximab (3), and MMF. MTX-LPD, the most common type of IA-LPD, is characterized by a high proportion of extranodal lesions, a high rate of Epstein Barr virus positivity in pathological tissues, and lymphoma that sometimes regresses spontaneously after withdrawal of suspected drugs (4).

In the present case, an extranodal lesion was found only in the lung, and spontaneous regression was observed after withdrawal of MMF. A PubMed search was performed to identify case reports of MMF-induced IA-LPD, excluding transplantation cases. Ten articles with 13 patients were identified (5-14) (Table 2). Lupus nephritis was the most common underlying disease. Most primary lesions were central nervous system lymphomas, and withdrawal of MMF as an initial treatment was reported in only 1 case (10). Among the 12 patients who received any treatment, treatment was effective in 8 (5, 7, 9, 11-13), best supportive care for disease progression was given to 1 patient (9), the outcome was not mentioned in 1 patient (6), and 2 patients died (8, 14). Ten patients were taking prednisolone concurrently, two patients were taking azathioprine, one was taking cyclophosphamide and cyclosporine, and one was taking no concomitant medications other than MMF. Inui et al. reported that patients with MTX-LPD who continued with other immunosuppressive or immunomodulatory therapy obtained tumor regression after MTX withdrawal (15). The present patient’s DM worsened after discontinuation of MMF, so MMF may have played an important role in her immunosuppression. Thus, it is difficult to judge whether or not the discontinuation of MMF contributed to her complete remission or whether a reduction in the degree of immunosuppression contributed to improvement of LPD.

According to some previous reports of MTX-LPD (15, 16), the ALC tends to be low at the diagnosis of MTX-LPD. After MTX withdrawal, lymphocyte recovery at two weeks is significantly greater in cases with tumor regression than in those without tumor regression. In the present case, the ALC was 1,008/μL at the start of MMF, did not decrease at the MMF-LPD diagnosis, and did not increase at 2 weeks after discontinuation of MMF (Table 1). In a previous review of the 13 patients identified in the 10 references, the ALC or white blood cell (WBC) count was mentioned in 10 patients. Among those 10 patients, the counts were decreased in 5 patients (7, 9, 10, 12, 14) and in the normal range in 5 patients (5, 8, 9, 11, 13). A change in the ALC after the start of treatment for MMF-LPD was reported in only one patient (7), and her reduced lymphocyte count had normalized. ALC recovery may thus contribute to spontaneous regression in MMF-LPD as it does in MTX-LPD, but it is difficult to reach a conclusion based solely on the present case report.

According to basic research, MTX inhibits DNA synthesis

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**Figure 2.** Histopathological findings of a transbronchial lung biopsy specimen. Hematoxylin and Eosin staining shows an aggregate of large atypical lymphocytes with heterogeneous chromatin and irregular nuclei (A). Immunohistochemistry shows positivity of B-cells for CD20 (B). Immunohistochemistry shows negativity for EBV-encoded small RNA (EBER) (C).
by inhibiting folate metabolism, and leukopenia appears as a side effect (17). In contrast, MMF inhibits only the de novo pathway, one of the purine synthesis pathways (18). Both T and B lymphocytes are mainly dependent on the de novo pathway for nucleic acid synthesis, so lymphocytopenia appears as a side effect. Therefore, given these mechanisms, MMF-LPD is also expected to cause lymphocytopenia.

Ichikawa et al. reported that 19 of 79 patients with MTX-LPD had begun chemotherapy after progression following withdrawal of immunosuppressant therapy (19). They showed that an Epstein-Barr virus (EBV)-positive and non-DLBCL status were important factors for regression, and age (>70 years old) and histological type of DLBCL were predictors of a shortened survival (19). Tokuhira et al. also reported that age over 70 years old was a factor associated with a poor prognosis, and the median duration before relapse in the regression of MTX-LPD group was 10.6 months (20). In contrast, Kurita et al. reported that the overall survival did not differ significantly between the subtype of MTX-LPD, and patients >70 years old had a better progression-free survival than those ≤ 70 years old (21). Although the prognostic factors in MMF-LPD remain controversial, the present patient was 76 years old, had DLBCL, and was EBV-negative; therefore, close follow-up by radiological examinations may be needed based on the previous reports of MTX-LPD. Regarding the follow-up duration, Gion et al. reported that the median follow-up duration of DLBCL type MTX-LPD was 16.9 months (22). In the present case, it has now been nine months since the discontinuation of MMF, so it will be necessary to follow her for an additional half year or more.

We believe that the Ann Arbor classification IE was an important factor influencing the occurrence of remission in the present case. Saito et al. reported that, among 20 patients who had remission, 10 were clinical stage I. Of 13 cases of persistent LPD, only 2 were stage I (16). Tokuhira et al. reported that there were no stage I cases among 13 cases of DLBCL-not otherwise specified (20). In the present case with DLBCL, the Ann Arbor classification was IE because the extranodal involvement was only in the lung. Thus, MMF was withdrawn without adding any other treatments, and a complete response was achieved, despite some factors associated with a poor prognosis.

In conclusion, when IA-LPD is suspected, the possibility that self-remission might occur should be considered in order to prevent unnecessary and possibly toxic treatments, such as radiation therapy or multi-drug chemotherapy. Furthermore, close long-term follow-up is needed to ensure that there is no progression.
**Table 2. Clinical Characteristics of Mycophenolate Mofetil-induced Lymphoproliferative Disorders in Previous Reports.**

| Characteristic | Our case | Patient1 | Patient2 | Patient3 | Patient4 | Patient5 | Patient6 |
|---------------|----------|----------|----------|----------|----------|----------|----------|
| Reference Number | - | 5 | 6 | 7 | 8 | 9 | 9 |
| Year | 2020 | 2004 | 2005 | 2005 | 2006 | 2007 | 2007 |
| Age (y) | 76 | 46 | 58 | 83 | 42 | 88 | 58 |
| Sex | Female | Female | Female | Female | Female | Female | Female |
| Underlying disease | DM | DM | LN | MG | LN | MG | CNS V |
| Duration of exposure to MMF | 2.5g/day | 1.5g/day | 1.0g/day | 1.0g/day | 1.0g/day | 1.0g/day | 1.0g/day |
| Concurrent other immunosuppression drugs | TAC, PSL | MTX, PSL | PSL | PSL | PSL | HCQ | |
| Lesion | lung | lung | CNS | CNS | CNS | CNS | CNS |
| Biopsy | Brain | Brain | EBV-associated B-cell lymphoma | EBV-positive diffuse large B cell lymphoma | B-cell lymphoma | diffuse large B-cell lymphoma | EBV-associated diffuse large B-cell lymphoma |
| Pathology | diffuse large B-cell lymphoma | EBV-positive diffuse large B cell lymphoma | EBV-positive lymphoma | EBV-positive lymphoma | EBV-positive lymphoma | EBV-associated lymphoma |
| EBV | negative | positive | positive | positive | positive | positive | positive |
| Treatment | DMX/RTX | DMX/RTX | DMX/RTX/Chemo | DMX/RTX | DMX/RTX | DMX/RTX |
| Response | CR | CR | NM | PR | Dead | CR | CR |
| Characteristic | Patient7 | Patient8 | Patient9 | Patient10 | Patient11 | Patient12 | Patient13 |
| Reference Number | 9 | 9 | 10 | 11 | 12 | 13 | 14 |
| Year | 2007 | 2007 | 2009 | 2010 | 2010 | 2011 | 2017 |
| Age | 65 | 57 | 69 | 42 | 43 | 41 | 56 |
| Sex | Male | Female | Female | Female | Female | Female | Female |
| Underlying disease | RP | DM | MG | AIH | LN | LN | LN |
| Duration of exposure to MMF | 1.0g/day | 1.0g/day | 1.5g/day | 0.5g/day | 3years | 8years | 2.0g/day |
| Concurrent other immunosuppression drugs | PSL, AZA | PSL, AZA | PSL | Nothing | PSL | CY, CsA | PSL, HCQ |
| Lesion | CNS | CNS | CNS | mouth | buccal and lingual lesion | CNS | CNS |
| Biopsy | Brain | Brain | ulcerated lesions | Brain | Brain | Brain | |
| Pathology | EBV-associated diffuse large B-cell lymphoma | EBV-associated polymorphous B-cell lymphoproliferative disorder | EBV-positive T-cell lymphoproliferative disorder | EBV-positive ILD of the Hodgkin-like variant | EBV driven large B-cell lymphoproliferative disorder | diffuse large B-cell lymphoma | |
| EBV | positive | positive | positive | positive | positive | negative | negative |
| Treatment | DMX/RTX | DMX/RTX | WD | RTX | MTX/RTX/RT | RTX/MPV/RT | MTX/RTX/TEM |
| Response | PD | CR | CR | CR | CR | CR | Dead |

AHI: autoimmune hepatitis, AZA: azathioprine, Chemo: chemotherapy, CNS: central nervous system, CR: complete response, CsA: cyclosporine A, CY: cyclophosphamide, DM: dermatomyositis, DMX: dexamethasone, EBV: Epstein-Barr virus, HCC: hydroxychloroquine sulfate, LN: lupus nephritis, MG: myasthenia gravis, MPV: methotrexate, vincristine, procarbazine, MTX: methotrexate, NM: no mention, PD: progressive disease, PSL: prednisolone, RP: relapsing polychondritis, RT: radiation therapy, RTX: rituximab, TAC: tacrolimus, TEM: temozolomide, WD: withdrawal

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

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375-2390.
2. Ellman MH, Hurwitz H, Thomas C, Kozloff M. Lymphoma developing in a patient with rheumatoid arthritis taking low dose weekly methotrexate. J Rheumatol 18: 1741-1743, 1991.
3. Kubica MG, Sangle NA. Iatrogenic immunodeficiency-associated lymphoproliferative disorders in transplant and nontransplant settings. Indian J Pathol Microbiol 59: 6-15, 2016.
4. Kim HJ, Ko YH, Kim JE, et al. Epstein-Barr virus-associated lymphoproliferative disorders: review and update on 2016 WHO Classification. J Pathol Transl Med 51: 352-385, 2017.
5. Waldman MA, Callen JP. Self-resolution of Epstein-Barr virus-associated B-cell lymphoma in a patient with dermatomyositis following withdrawal of mycophenolate mofetil and methotrexate. J
6. Dasqupta N, Gelber AC, Rakee F, Fine DM. Central nervous system lymphoma associated with mycophenolate mofetil in lupus nephritis. Lupus 14: 910-913, 2005.
7. Vernino S, Salomao DR, Habermann TM, O’Neill BP. Primary CNS lymphoma complicating treatment of myasthenia gravis with mycophenolate mofetil. Neurology 23: 639-641, 2005.
8. Finelli PF, Naik K, DiGiuseppe JA, Prasad A. Primary lymphoma of CNS, mycophenolate mofetil and lupus. Lupus 15: 886-888, 2006.
9. O’Neill BP, Vernino S, Dogan A, Giannini C. EBV-associated lymphoproliferative disorder of CNS associated with the use of mycophenolate mofetil. Neuro Oncol 9: 364-369, 2007.
10. Dubal DB, Mueller S, Ruben BS, Enqstrom JW, Josephson SA. T-cell lymphoproliferative disorder following mycophenolate treatment for myasthenia gravis. Muscle Nerve 39: 849-850, 2009.
11. Adams B, Lazarchick J, Medina AM, et al. Iatrogenic immunodeficiency-associated lymphoproliferative disease of the Hodgkin lymphoma-like variant in a patient treated with mycophenolate mofetil for autoimmune hepatitis. Am J Hematol 85: 627-629, 2010.
12. Tsang HH, Trendell-Smith NJ, Wu AK, Mok MY. Diffuse large B-cell lymphoma of the central nervous system in mycophenolate mofetil-treated patients with systemic lupus erythematosus. Lupus 19: 330-333, 2010.
13. Svobodova B, Hruskova Z, Rysava R, Tesar V. Brain diffuse large B-cell lymphoma in a systemic lupus erythematosus patient treated with immunosuppressive agents including mycophenolate mofetil. Lupus 20: 1452-1454, 2011.
14. Balci MA, Pamuk GE, Unlu E, Usta U, Pamuk ON. Development of primary central nervous system lymphoma in a systemic lupus erythematosus patient after treatment with mycophenolate mofetil and review of the literature. Lupus 26: 1224-1227, 2017.
15. Inui Y, Matsuoka H, Yakushiji K, et al. Methotrexate-associated lymphoproliferative disorders: management by watchful waiting and observation of early lymphocyte recovery after methotrexate withdrawal. Leuk Lymphoma 56: 3045-3051, 2015.
16. Saito S, Kaneko Y, Yamaoka K, Tokuhira M, Takeuchi T. Distinct patterns of lymphocyte count transition in lymphoproliferative disorder in patients with rheumatoid arthritis treated with methotrexate. Rheumatology (Oxford) 56: 940-946, 2017.
17. Walling J. From methotrexate to pemetrexed and beyond: a review of the pharmacodynamic and clinical properties of antifolates. Invest New Drugs 24: 37-77, 2006.
18. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 47: 85-118, 2000.
19. Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression. Eur J Haematol 91: 20-28, 2013.
20. Tokuhira M, Saito S, Okuyama A, et al. Clinicopathologic investigation of methotrexate-induced lymphoproliferative disorders, with a focus on regression. Leuk Lymphoma 59: 1143-1152, 2018.
21. Kurita D, Miyoshi H, Ichikawa A, et al. Methotrexate-associated lymphoproliferative disorders in patients with rheumatoid arthritis: clinicopathologic features and prognostic factors. Am J Surg Pathol 43: 869-884, 2019.
22. Gion Y, Iwaki N, Takata K, et al. Clinicopathological analysis of methotrexate-associated lymphoproliferative disorders: comparison of diffuse large B-cell lymphoma and classical hodgkin lymphoma types. Cancer Sci 108: 1271-1280, 2017.

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