Myasthenia Gravis Complicated with Peripheral T-cell Lymphoma, Not Otherwise Specified (PTCL-NOS), Following Thymectomy and Longstanding Tacrolimus Therapy

Masahiro Ohara¹, Kokoro Ozaki¹, Takuya Ohkubo¹, Akane Yamada¹, Yoshiyuki Numasawa¹, Keisuke Tanaka², Shohei Tomii³, Satoru Ishibashi¹, Nobuo Sanjo¹ and Takanori Yokota¹

Abstract:
Myasthenia gravis (MG), a neuromuscular junction autoimmune disease, sometimes complicates second malignancies; however, T-cell lymphoproliferative disorders have rarely been reported. A 55-year-old man, who received oral tacrolimus and prednisolone for MG for 16 years after thymectomy, presented with left abdominal pain, lymphadenopathy, and splenomegaly. A lymph node biopsy revealed peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). This is the first report of oral tacrolimus leading to a T-cell lymphoproliferative disorder in patient without a history of transplantation. Physicians should be aware of the possibility of rare T-cell lymphoproliferative disorders, such as PTCL-NOS, occurring as complications in MG patients on immunosuppressive regimens after thymectomy.

Key words: myasthenia gravis, lymphoma, PTCL-NOS, tacrolimus, thymectomy

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Introduction
Myasthenia gravis (MG) is an autoimmune disease that disrupts the function of the neuromuscular junction through autoantibodies against the acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) (1). Peripheral T-cell lymphomas (PTCLs) represent 10-15% of non-Hodgkin lymphomas, and are classified into 23 different entities, encompassing various heterogeneous diseases (2). Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is the second most prevalent variant of PTCL; the coexistence of MG with T-cell non-Hodgkin lymphoma is very rare and only a few case reports have been reported. Among the cases complicated with a thymoma, most suffered from T-lymphoblastic leukemia/lymphoma (3). We herein report the case of a patient undergoing long-term treatment with a calcineurin inhibitor for MG who developed PTCL-NOS 16 years after thymectomy. We discuss the causal relationship among MG, oral tacrolimus (TAC) and PTCL-NOS in the current case, with reference to previous cases.

Case Report
A 55-year-old man was hospitalized for left abdominal pain. The patient had previously been diagnosed with MG (MGFA classIIa) and had undergone thymectomy at 39 years of age. The thymus was pathologically normal. He had since been treated with oral TAC and prednisolone (PSL) for 16 years. On admission, a physical examination revealed tenderness in the left upper abdomen, a palpable spleen and bilateral lymphadenopathy in the neck, left sub-
mandibular region, and right groin that were associated with spiking fever and night sweats. A neurological examination revealed bilateral ptosis and diplopia. Laboratory tests revealed the following: a normal white blood cell count (5,400/μL; reference range, 3,600-9,300/μL); a decreased platelet count (9.3×10^5/μL; reference range, 12-41×10^5/μL); elevated lactate dehydrogenase (432 U/L; reference range, 109-210 U/L), anti-AChR antibody positivity (0.6 nmol/L; reference range, <0.2 nmol/L); an extremely elevated serum soluble interleukin 2 receptor level (16,600 U/mL; reference range, <145 U/mL). Systemic computed tomography (CT) revealed bilateral ptosis and diplopia. Laboratory tests revealed the following: a normal white blood cell count.

Discussion

We treated a patient with MG who developed PTCL-NOS after thymectomy and subsequent long-term oral immunosuppressive treatment. There are very few previous reports of MG complicating T-cell lymphoma; this is the second report of MG with PTCL-NOS. Although Cory et al. reported a case of concurrent MG, thymoma, and PTCL-NOS (3), this report presents the first case of PTCL-NOS occurring after long-term immunosuppressive treatment for non-thymomatous MG after thymectomy. There could be several explanations for the pathogenic etiology and mechanisms of PTCL-NOS in our case.

First, one plausible explanation is that longstanding immunosuppressive treatment for 16 years may have weakened the antitumor immune responses, resulting in the occurrence of PTCL-NOS. TAC binds to the FK-binding protein (FKBP) in helper T cells (4); this complex acts on intracellular phosphatase calcineurin, and subsequently inhibits the activation of nuclear factor of activated T cells (NFAT), resulting in the suppression of cytokine production (e.g., IL-2, IL-5, and IL-6) and immune reactions (4). Immunological responses, especially the activity of natural killer cells and cytotoxic T-cells, against cancerous tumor cells are weakened by the suppression of cytokine production, sometimes resulting in the development of malignancy (4). Thus, it is proposed that oral TAC may cause malignant lymphomas in post-transplantation patients (5-8). The association between oral TAC and malignant lymphomas without a history of transplantation has only been reported in 3 cases; however, it is possible that oral TAC generally leads to the development of lymphoproliferative disorders (Table 1) (9-11). These cases all involved B-cell lymphomas. The present study is the first report describing the development of PTCL-NOS in an MG patient on longstanding oral TAC treatment. Cyclosporine, another calcineurin inhibitor, is also known to cause B-cell lymphomas, but very rarely T-cell lymphomas (16, 17). There is only one case in which primary cutaneous CD30+ large T-cell lymphoma was reported to have developed after cyclosporine treatment for psoriasis (Table 1) (12). In addition, it was reported that the experimental use of oral pimecrolimus, a calcineurin inhibitor, increased the incidence of pleomorphic or malignant lymphomas in CD-1 mice (18, 19). Thus, it is likely that longstanding immunosuppression by TAC induced PTCL-NOS in this case.
case. Moreover, the sustained stimulation of lymphocytes by autoantigens may drive cellular proliferation and result in the development of malignant lymphoma. Some autoimmune diseases are known to lead to malignancies long after their diagnosis, and chronic autoimmune diseases such as rheumatoid arthritis, Sjögren’s syndrome, and systemic lupus erythematosus increase the risk of developing malignant disease, especially malignant lymphoma (20). In these diseases, it is proposed that mechanisms underlying sustained autoantigen stimulation drive lymphocytic proliferation (21, 22). Colon cancer, breast cancer, and malignant lymphoma are extrathymic malignancies that are frequently reported in MG (23); there have been only 6 reports on complications of T-cell lymphoproliferative disorders in the literature (Table 2) (3, 24-28). In 3 of these cases, chemotherapy for T-cell lymphoblastic lymphoma (T-LBL) was also effective against MG; in 2 of them, the complete remission of MG and T-LBL was achieved (24-26). In these cases, MG may have presented as one of the paraneoplastic neurological syndromes induced by lymphoma. In contrast, in our case a paraneoplastic etiology is unlikely because MG was diagnosed as long as 16 years before PTCL-NOS. Interestingly, however, there is an argument that MG may be protective against second cancers. Owe et al. observed that patients with MG showed a lower incidence of cancer in comparison to the normal population (29). Thus, it is controversial whether MG causes second malignancies, particularly lym-

### Table 1. Case Reports of Lymphoproliferative Disorders after Oral Calcineurin Inhibitors Use without History of Transplantation.

| References | Age/Sex | Type of lymphoproliferative disorders | Type of calcineurin inhibitors | Oral calcineurin inhibitors dose/Administration period | Primary disease | EBV infection |
|------------|---------|--------------------------------------|--------------------------------|-------------------------------------------------------|----------------|--------------|
| 12         | 61/F    | LTCL                                 | CsA                            | 3 mg/kg/day, 8 years                                   | Psoriasis      | N.A.         |
| 13         | 67/M    | BL                                   | CsA                            | 5 mg/kg/day, 8 months                                  | Psoriasis      | N.A.         |
| 14         | 58/M    | BL                                   | CsA                            | 2.5-5 mg/kg/day, 4 years                               | RA             | Negative     |
| 15         | 37/M    | CD30+large cell lymphoma             | CsA                            | 2.5-4 mg/kg/day, 1 year                                | AD             | N.A.         |
| 16         | 70/M    | NHL                                  | CsA                            | 3.3 mg/kg/day, 21 months                               | Refractory anemia | Negative     |
| 17         | 33/M    | NHL                                  | CsA                            | 200 mg/kg/day, 4 years                                 | UC             | N.A.         |
| 9          | 69/F    | DLBCL                                | TAC                            | 3 mg/day, 14 months                                   | SS/MCTD        | Negative     |
| 10         | 74/F    | BL                                   | TAC                            | N.A., 32 months                                       | RA             | N.A.         |
| 11         | 73/M    | LPL                                  | TAC                            | N.A., 10 months                                       | MG             | N.A.         |
| The present case | 55/M | PTCL-NOS                           | TAC                            | 3 mg/kg/day, 16 years                                  | MG             | Negative     |

M: male; F: female; SS: Sjögren’s syndrome, MCTD: mixed connective tissue disease, RA: rheumatoid arthritis, MG: myasthenia gravis, AD: atopic dermatitis, UC: ulcerative colitis, N.A.: not available, TAC: tacrolimus, CsA: cyclosporine, DLBCL: diffuse large B-cell lymphoma, BL: Burkitt lymphoma, LPL: lymphoplasmacytic lymphoma, LTCL: large T-cell lymphoma, NHL: non-Hodgkin’s lymphoma, PTCL-NOS: peripheral T-cell lymphoma: not otherwise specified

### Table 2. Case Reports of MG with T-cell Lymphoproliferative Disorders.

| References | Age/Sex | Lymphoma/ Leukemia type | When T-cell lymphoproliferative disorders diagnosed | Treatment of T-cell lymphoproliferative disorders/ Response of MG to the treatment |
|------------|---------|-------------------------|-----------------------------------------------|-------------------------------------------------------------------------|
| 24         | 51/F    | T-LBL                   | 1 year after MG diagnosis                      | CT/ Complete remission of lymphoma and MG for 1 year                     |
| 25         | 51/F    | T-LBL                   | 2-3 months after MG diagnosis                  | CT/ Complete remission of lymphoma and MG for 2 years                    |
| 26         | 38/M    | T-LBL                   | 1 year after MG diagnosis                      | CT/ Remission of lymphoma and MG initially, but relapse of MG and lymphoma 5 and 6 years after initial diagnosis |
| 27         | 26/M    | T-LBL                   | a few months before MG diagnosis               | CT/ Death due to progressive lymphoma                                     |
| 28         | 43/M    | T-cell lymphoblastic leukemia | 6 years after MG diagnosis                     | CT/ Death due to progressive lymphoma                                     |
| 3          | 59/F    | PTCL-NOS                | Simultaneous                                   | CT/ Death due to infection during CT                                      |
| The present case | 55/M | PTCL-NOS              | 16 years after MG diagnosis                    | CT/ Partially remission of lymphoma, but no improvement of MG symptoms |

M: male; F: female; T-LBL: T-cell lymphoblastic lymphoma, PTCL-NOS: Peripheral T-cell lymphoma: not other specified, MG: myasthenia gravis, CT: chemotherapy
phoid malignancy. Large and controlled studies should be performed to assess whether longstanding MG predisposes patients to lymphoid malignancies.

The present case suggests that it is possible that longstanding oral TAC treatment and sustained autoantigen stimulation drove lymphocytic proliferation.

**Conclusion**

A case of MG was complicated by PTCL-NOS following long-term oral TAC treatment after thymectomy. The association between MG and PTCL-NOS is complex, and the long-term use of immunosuppressive therapy as well as sustained autoantigen stimulation may have affected the development of PTCL-NOS in the present case.

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

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