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【 CASE REPORT 】

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

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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-

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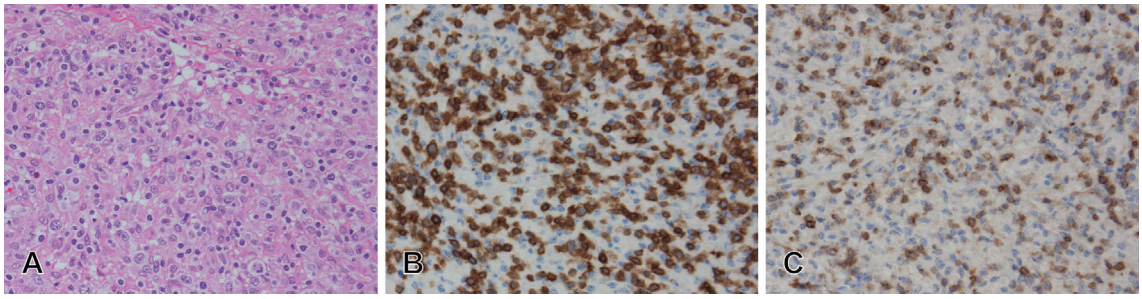

Figure. The histological findings of an inguinal lymph node biopsy specimen. Diffuse proliferation of atypical small- or medium-sized lymphoid cells were shown on Hematoxylin-Eosin staining sections (A; original magnification, 200 ×). These cells were positive for CD3 (B; 200 ×), but the expression of CD7 was diminished (C; 200 ×).

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 (9.3×10^4/μL; reference range, $12\text{-}41\times10^4$/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 right inguinal lymphadenopathy and low-density areas in the enlarged spleen. Because these findings suggested malignant lymphoma, a right inguinal lymph node biopsy was conducted; the diffuse proliferation of atypical small- or medium-sized lymphoid cells was observed, and immunostaining revealed that the proliferating cells expressed CD3, CD5, CD4<8, with the diminished expression of CD7. The proliferating cells did not express CD20/CD79a (Figure). A clinical staging examination of the bone marrow showed hypercellular marrow with infiltrating lymphoma cells that were positive for CD3. Flow cytometry of the marrow aspirate demonstrated an abnormal T-cell population that expressed CD2, CD3, CD4, CD5, CD7, and CD8. Myeloid and B-cell markers, as well as CD1a, CD16, CD25, CD56, and TdT, were absent. Although the differential diagnosis of CD4-positive/CD8-positive T-cell lymphoma includes T-lymphoblastic leukemia/lymphoma, T-cell prolymphocytic leukemia, and PTCL-NOS, the overall morphologic, immunophenotypic, and cytogenetic findings were most consistent with PTCL-NOS. Epstein-Barr virus (EBV) was not identified in the tumor cells by EBV-encoded RNA *in situ* hybridization. The patient's serum was negative for human T-cell leukemia virus types 1 and 2. We discontinued TAC to allow the recovery of the antitumor immune responses and started combined chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP therapy), which elicited a partial response.

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.,* TL-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

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	positive
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/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/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

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-

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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