

# Myasthenia gravis appearing after thymectomy for thymoma

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## Abstract

**Objective:** A few thymoma patients without myasthenia gravis (MG) have been observed to develop MG after total removal of the thymoma (postoperative MG). However, the cause of this is not yet known because of the rarity of postoperative MG patients. This study evaluated the clinical characteristics of the 8 postoperative MG patients. **Methods:** We compiled 1089 thymoma patients treated between 1990 and 1994 in 115 institutes in Japan, and found 8 cases of postoperative MG. **Results:** Postoperative MG was found in 8 (0.97%) of 827 thymoma patients without preoperative MG. The postoperative MG patients included 1 male and 7 females, with a mean age of  $50.5 \pm 15.0$  years. The thymoma was completely resected in all cases. The surgical method used was extended thymectomy in 2 cases and thymothymectomy in 6 cases. There were 2 cases (0.7%) of postoperative MG in the extended thymectomy group ( $n=275$ ), 6 (1.9%) in the thymothymectomy group ( $n=321$ ), and none in the tumor resection group ( $n=137$ ). The interval between thymectomy and the onset of postoperative MG varied (6 days-45 months,  $19.3 \pm 16.5$  months). The type of MG was ocular in 2 cases and general in 5 cases, according to the modified Osserman classification. The postoperative MG was responsive to anti-cholinesterase compounds and/or steroids. The improvement rate was 86%. **Conclusions:** Postoperative MG was present in about 1% of the patients who underwent total thymoma resection. Resection of the thymus gland does not prevent postoperative MG.

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**Keywords:** Thymoma; Myasthenia gravis; Postoperative; Thymectomy

## 1. Introduction

Thymoma is an uncommon neoplasm that is derived from the epithelial cells of the thymus. It is well known due to several interesting features, including its association with myasthenia gravis (MG) and other autoimmune diseases, its histological variability, and the heterogeneity of its malignant behavior [1,2]. MG is an autoimmune disease in which the clinical features, muscular weakness and fatigability of skeletal muscles, are known to be caused by an autoimmune antibody against the acetylcholine receptor at the neuromuscular junction [3]. Thymoma occurs in approximately 10% of patients with MG and, in turn, MG occurs in approximately one-third of patients with thymoma [4]. It has long been suspected that the thymus or thymoma may play a role in the pathogenesis of MG.

In thymoma patients without MG, a few have developed MG after total removal of the thymoma [5-8]. We defined cases of MG onset after total removal of the thymoma as

'postoperative MG', and were interested in evaluating the relationships among MG, thymoma, and the adjacent thymus. However, there has been little information regarding postoperative MG in the literature. It has been said in previous reports that the onset of MG after total thymoma removal occurs in 1.5-28% of cases without MG [9-11].

We compiled 1093 thymoma patients treated between 1990 and 1994 in 115 institutes in Japan, and found 8 cases of postoperative MG [12,13]. This study evaluated the clinical characteristics of the 8 postoperative MG patients.

## 2. Material and methods

### 2.1. Patients

We sent a questionnaire on thymic epithelial tumors to 185 institutes certified as special institutes by the Japanese Association for Chest Surgery, and received replies from 115 institutes (62%). We compiled 1093 thymoma patients who were treated between 1990 and 1994. The thymoma patients included 495 males and 590 females. The patients' ages ranged from 8 to 94 years with a mean age of  $53.7 \pm 14.0$  years. The thymomas were subclassified according to a modification of Bernatz's classification into the following types: predominantly lymphocytic thymoma (PL-thymoma,  $n=344$ ), predominantly epithelial thymoma (PE-thymoma,  $n=226$ ), mixed thymoma ( $n=428$ ), and spindle cell thymoma ( $n=41$ ) [14]. In this study, pathologists certified by

**Abbreviations:** MG, myasthenia gravis; postoperative MG, MG onset after total removal of the thymoma; PL-thymoma, predominantly lymphocytic thymoma; PE-thymoma, predominantly epithelial thymoma; PRCA, pure red cell aplasia.

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the Japanese Society of Pathology in each institute made diagnoses of thymoma, thymic carcinoma, or thymic carcinoid. The final pathological staging was performed based on Masaoka's staging system [15]. The severity of MG disease was classified according to modified Osserman classification: type I, MG limited to the ocular region only; type IIa, mild generalized MG; type IIb, severe generalized MG; and type III, acute fulminating MG [16]. The surgical method for thymoma was classified into three groups: extended thymectomy (resection of the thymoma, thymus, and the anterior mediastinal adipose tissue around the thymus), thymothymectomy (resection of the thymoma and thymus), and tumor resection (resection of the tumor and a portion of the thymus) [17].

### 3. Results

#### 3.1. Complication rate of thymic epithelial tumors

There were no statements regarding MG in 4 of the thymoma patients. MG was associated with 270 (24.8%) of the 1089 thymoma cases, including the 8 postoperative MG cases. Pure red cell aplasia (PRCA), including 4 cases of postoperative PRCA, hyper- or hypoglobulinemia, and Sjögren's syndrome were associated with 28 cases (2.6%), 7 cases (0.65%), and 5 cases (0.46%) of thymoma, respectively.

#### 3.2. Patients with MG appearing after thymectomy for thymoma

Postoperative MG was associated with 8 (0.97%) of the 827 thymoma patients without preoperative MG. These 8 cases are listed in Tables 1 and 2. They included 1 male and 7 females, ranging from 32 to 79 years of age with a mean age of  $50.5 \pm 15.0$  years. The 8 cases consisted of 5 cases of PL-thymoma, 2 cases of mixed thymoma, and 1 case of PE thymoma. The distribution of the Masaoka clinical stage showed 2 in stage I, 4 in stage II, 1 in stage III, and 1 in stage IVa. The thymoma was completely resected in all cases. The surgical method employed was extended thymectomy in 2 cases and thymothymectomy in 6 cases. There were 2 cases (0.7%) of postoperative MG in the extended thymectomy group ( $n=275$ ), 6 (1.9%) in the thymothymectomy group ( $n=321$ ), and none in the tumor resection group ( $n=137$ ). The interval between thymectomy and the onset of MG

ranged from 6 days to 3 years and 9 months ( $19.3 \pm 16.5$  months). The type of MG was ocular in 2 cases and general in 5 cases according to modified Osserman classification. In 4 cases, the anti-acetylcholine receptor antibodies were measured preoperatively, and were found to be elevated in only 1 case (9.0 nmol/l). In 7 of the patients with postoperative MG, 6 were treated with anti-cholinesterase or steroids, and 5 improved (2 with remission and 3 with improvement). The other 1 patient remitted without treatment.

#### 3.3. Patients with PRCA appearing after thymectomy for thymoma

Postoperative PRCA included 2 males and 2 females, ranging from 25 to 66 years of age, with a mean age of  $49.0 \pm 17.6$  years. The 4 cases consisted of 3 cases of PL-thymoma, and 1 case of mixed thymoma. The distribution of the Masaoka clinical stage was 1 in stage I, 2 in stage III, and 1 in stage IVa. The thymoma was completely resected in 3 cases and the only disseminated lesions remained in 1 case. One of the 3 completely resected cases experienced recurrence (dissemination). The surgical method employed was extended thymectomy in 2 cases and thymothymectomy in 2 cases. The interval between thymectomy and the onset of PRCA was 5 months, 6 and 8 years (1 case was unknown).

### 4. Discussion

MG occurred in 25% of the patients with thymoma in this study, as shown in previous studies [4]. It has been said in previous reports that the onset of MG after total thymoma removal occurred in 1.5-28% of cases of thymoma without MG [9-11]. Of these reports, the reports by Namba and Ito had an adequate number of cases and detailed clinical data [9,11]. The clinical characteristics of postoperative MG patients in 3 studies are shown in Table 3. Namba et al. reported 33 postoperative MG cases including 7 of their own cases, and suggested that they accounted for about 3% of thymoma patients without MG [9]. Ito et al. reported 13 (3.3%) postoperative MG cases out of 394 cases of thymoma without MG [11]. Our study showed 8 (0.97%) postoperative MG cases out of 827 thymoma cases without preoperative MG. Our study showed female dominance, although Namba and Ito reported only slight to equal dominance (male:female=14:18, 7:6) [9,11]. The histological types

Table 1  
Clinical characteristics of postoperative MG cases (1)

Patient	Gender	Age	Diagnosis	Histological subtype	Stage <sup>a</sup>	Surgical method	Adjuvant therapy	Recurrence
1	m	79	Thymoma	PE	I	Thymectomy	None	None
2	f	53	Thymoma	Mixed	II	Extended thymectomy	None	None
3	f	34	Thymoma	Mixed	III	Thymectomy	None	None
4	f	54	Thymoma	PL	IVa	Extended thymectomy	Chemotherapy	Unknown
5	f	32	Thymoma	PL	I	Thymectomy	None	None
6	f	57	Thymoma	PL	II	Thymectomy	Radiotherapy	None
7	f	53	Thymoma	PL	II	Thymectomy	None	None
8	f	42	Thymoma	PL	II	Thymectomy	None	None

m, male; f, female; PE, predominantly epithelial; PL, predominantly lymphocytic; MG, myasthenia gravis.

<sup>a</sup> Masaoka clinical stage.

Table 2  
Clinical characteristics of postoperative MG cases (2)

Patient	Period between operation and onset (months)	Osserman <sup>a</sup>	Preoperative anti-AChR antibody (pmol/l)	Anti-AChR antibody at onset (pmol/l)	Therapy for MG			Result	Prognosis
					Surgical method	Steroid	Anti-cholinesterase		
1	1	IIA	Not done	91	None	Predonine	None	Remission	Dead
2	12	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
3	6 days	IIA	<0.2	15	None	Predonine	Mytelase, mestinon	Improve	Alive
4	31	I	Not done	76	None	None	None	Remission	Alive
5	45	IIB	<0.2	7	None	None	Mytelase	Improve	Alive
6	31	I	<0.2	1.8	None	None	Mestinon	Remission	Alive
7	4	IIA	9.0	30.9	None	Predonine	None	No change	Alive
8	12	IIA	Not done	10.1	None	Predonine	None	Improve	Alive

AChR, anti-acetylcholine receptor.

<sup>a</sup> Osserman classification.

(63% in mixed type, 25% in PL type, 12% in PE type, and none in spindle cell type) in this study were similar to those in previous reports (65%, 70% in the mixed type; 22%, 15% in the PL type; 13%, 15% in the PE type; and none in the spindle cell type, respectively) [9,11]. The distribution of histological type was similar to that in the patients with thymoma and preoperative MG.

The frequencies of postoperative MG cases in this study were 1.9 and 0.7% in the thymothymectomy and extended thymectomy groups, respectively. On the other hand, there were no cases in the tumor resection only group. Ito et al. demonstrated that there were more postoperative MG cases in the thymothymectomy group (3.9%, 7/178) than in the tumor resection only group (2.8%, 6/211) [11]. These data suggest that resection of the thymus gland does not prevent postoperative MG.

The interval between thymectomy and the onset of postoperative MG varied between this study (from 6 days to 45 months, with a mean of 19 months), Namba's study (from 2 weeks to 72 months, with a mean of 18 months), and Ito's study (from 0 to 117 months, with a mean of 24 months) [9,11]. Although Namba et al. reported that the interval between thymectomy and onset of postoperative MG was longer in patients whose condition subsequently worsened or stayed the same than in those who went into remission, both ours and Ito's study found no such a tendency [9,11].

As all postoperative MG patients underwent thymothymectomy or extended thymectomy, treatment for postoperative MG consisted of anti-cholinesterase compounds and/or steroids. The improvement rate was 86%, including 1 case of spontaneous remission. In Ito's study, 3 of the 6 patients with tumor resection only underwent thymectomy after the onset of postoperative MG. Eight of the 12

patients used steroids and the improvement rate was 83% [11]. In Namba's study, treatment for postoperative MG consisted only of anti-cholinesterase compounds, and the improvement rate was 40%. This was better than the improvement rate of the myasthenic patients with thymoma (26%), and almost equal to those without thymoma (42%) [9]. These data demonstrate that postoperative MG is responsive to anti-cholinesterase compounds and/or steroids, and that the prognosis is relatively good. Although thymectomy does not prevent the onset of postoperative MG, the patients who underwent thymectomy showed a good prognosis. We recommend thymothymectomy or extended thymectomy as a surgical procedure for the patients with thymoma.

The mechanism of the onset of postoperative MG is unclear. Considering the various time periods between thymectomy and the onset of postoperative MG, it is difficult to consider that thymectomy directly triggers MG onset. Recently, two appealing studies were published. Hoffacker et al. demonstrated that thymoma releases mature autoantigen-specific T-cells into the periphery, using T-cell proliferation assays for a fragment of the acetylcholine receptor, the midsize neurofilament protein, and tetanus toxoid [18]. Buckley et al. reported that T-cells in the thymoma are exported to the peripheral blood, and that these T-cells can persist in the periphery for many years, by measuring T-cell receptor excision circles that are generated by T-cell receptor gene rearrangement [19]. These studies suggest that thymoma actively exports large numbers of mature T-cells into the peripheral blood and that, following export, the cells persist in the periphery, potentially stimulating autoantibody production and subsequent autoimmune disease.

Table 3  
Clinical characteristics of postoperative MG in 3 studies

Study	Number of case	Incidence rate (%)	Male: female	Histological type				Surgical procedure			Interval		Improvement rate (%)
				PL (%)	Mixed (%)	PE (%)	Spindle (%)	Ex-thym (%)	Thym (%)	Tumor (%)	Period	Mean	
Namba	33	3	14:18	22	65	13	0	-	-	-	2 w-72 m	18 m	40
Ito	13	3.30	7:6	15	70	15	0	-	3.90	2.80	0-117 m	24 m	83
Present	8	0.97	1:7	25	63	12	0	0.70	1.90	0	6 d-45 m	19 m	86

PL, predominantly lymphocytic thymoma; mixed, mixed thymoma; PE, predominantly epithelial thymoma; spindle, spindle cell thymoma; ex-thym, extended thymectomy; thym, thymothymectomy; tumor, tumor resection; interval, interval between thymectomy and onset of postoperative MG; w, week; m, month; d, day.

In conclusion, the onset of MG after total thymoma removal occurred in 1-3% of thymoma patients without MG. Although the resection of the thymus gland does not prevent the onset of postoperative MG, the patients who underwent thymectomy showed a good prognosis. We recommend thymothymectomy or extended thymectomy as a surgical procedure for thymoma patients without MG.

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