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Extrathymic malignancies in patients with myasthenia gravis

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Abstract

Introduction: Myasthenia gravis (MG) is considered a paraneoplastic phenomenon of thymomas in 15% of patients. Co-existence of MG with extrathymic malignancies, and an increased risk of second malignancy in patients with thymoma have been reported. Data on clinical characteristics of MG patients with extrathymic malignancies and the role of concomitant diseases and their treatment are lacking.
Methods: The clinical records of 188 consecutive MG patients were studied retrospectively. We examined whether gender, age, generalized disease, seropositivity for acetyl-choline receptor antibodies, occurrence of thymoma, immunosuppressive therapy and occurrence of other autoimmune diseases determined an increased risk for development of extrathymic malignancy.
Results: This group followed the typical epidemiological characteristics of MG. Thirty-three patients (17.6%) had a thymoma. Twenty-nine patients (15.4%) had 30 extrathymic malignant tumors of various origins. Only four patients with extrathymic tumors had an associated thymoma. Tumors were diagnosed between 20 years prior to and 35 years after the appearance of MG. Older age of MG onset was the only risk factor identified for development of malignancy in MG.
Discussion: Extrathymic malignancies are common in MG patients, especially in the older age group. There are no specific clinical features of the subgroup of MG patients with cancer. Although MG is not a paraneoplastic phenomenon of extrathymic malignancy, the association between MG and malignancy may be due to a common background of immune dysregulation.

Keywords: Myasthenia gravis; Cancer; Thymoma; Autoimmune disease; Azathioprine

1. Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disease, which affects both young and elderly individuals. MG is considered a paraneoplastic phenomenon of thymomas in 15% of patients. Extrathymic malignancies have been also reported to coincide with MG [1–4]. An association with malignancy, especially of hematological origin, has been observed in several other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythomatosus, inflammatory myopathies, scleroderma, Sjogren's syndrome and thyroiditis [5,6]. In addition, patients with thymoma may have an increased risk for second malignancy [7,8]. The specific clinical features of MG patients that are prone to develop cancer are not known. We retrospectively studied the frequency, type and time of appearance of malignant tumors in our cohort of MG patients. We also examined whether appearance of extrathymic malignancy was related to certain clinical features of MG, to its treatment, to the presence of thymomas or to the patients' tendency for autoimmunity, other than MG.

2. Methods

The clinical records of 188 consecutive patients with confirmed diagnosis of MG according to Seybold criteria for "definite MG with typical presentation" [9] that were

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Table 1
Co-incidence of myasthenia gravis with malignant tumors

Myasthenia gravis				Cancer				
Age of onset/sex	Type/serology	Treatment	Thymoma	Age	Type	Treatment	Follow-up	Mutual effect
A								
32/F	Gen/+	Pred	–	65	Ca of breast	Chemotherapy	Met (1 year)	
68/F	Gen/+	Pred, Aza	+	64	Breast Can (lt)			
				72	Breast Ca (rt)	Tamoxifen	NED (7 years)	
57/M	Gen/+	Pred, Aza	–	73	Ca of colon	Surgery	NED (1 year)	Exacerbation with the diagnosis of malignancy
62/M	Gen/+	Pred, Aza	–	78	Kaposi sarcoma			
73/F	Gen/+	Pred	–	81	Metastatic chordoma of sacrum	Radiotherapy	Local recurrence (3 years)	
61/F	Gen/+	Pred, Aza, PEx	+	67	Ca of colon	Surgery	NED (8 years)	
50/F	Gen/+	Pred, Aza	–	59	Ca of nasal cavity	Surgery, brachytherapy	NED (2 years)	
18/F	Gen/+	Pred, Aza, PEx, Cyclo	–	39	Ca of colon	Surgery	NED (6 years)	
18/M	Gen/+	Thymectomy	–	19	Mixed germ cell tumor	Surgery, chemotherapy	Met (3 years)	MG improved with chemotherapy
70/F	Gen/+	Pred, PEx	–	>70	CLL		Exitus	
38/F	Gen/+	Aza, PEx, IvIg	+	47	Ca of breast	Tamoxifen, chemotherapy, radiotherapy	Recurrence (1 years) Exitus (2 years)	
21/M	Gen/+	Thymectomy	–	56	Hepatic cell Ca		Met	Infected by HCV during thymectomy. MG exacerbated 3 years before hepatoma
38/F	Gen/–			51	Ca of breast	Surgery, radiotherapy	NED (5 years)	
24/F	Gen/+	Pred, Aza, PEx	–	>24	GBM	Chemotherapy, radiotherapy	Exitus (1 year)	Improvement in MG after tumor appearance
5.5/F	Ocular/–	Thymectomy	–	29	Glioma	Surgery	Exitus (4 years)	
50/F	Gen/–		–	65	Ca of breast	Surgery		Mild MG exacerbation before surgery
32/F	Gen/+	Pred, Aza, Thymectomy	–	64	Melanoma			
70/M	Gen/+	Aza, PEx	–	80	Gastric lymphoma	Exacerbation with the diagnosis of malignancy		
52/M	Gen/+	Aza	–	64	SCC of tongue	Surgery		
42/F	Gen/+	Aza	+	67	Merkell cell carcinoma	Surgery		
61/M	Gen/+	PEx, Aza	–	67	Ca of colon	Surgery		
68/M	Gen/+	Pred, Aza, Pex ,IvIg	–	74	Ca of pancreas	Surgery		
B								
50/M	Gen/+	Pred, Aza, PEx	–	42	Renal cell Ca	Surgery	Lung mets (8 years)	Lung met were diagnosed close to MG
61/F	Gen/+		–	41	Ca of breast		NED (22 years)	
66/F	Gen/+	Gen/+	–	64	Ca of breast	Surgery, radiotherapy	NED (6 years)	
64/M	Gen/+		–	<64	Melanoma		Exitus	
59/M	Gen/+	Aza	–	51	Ca of breast	Surgery, radiotherapy	NED (9 years)	
73/F	Gen/+	Aza, PEx,	–	68	Ca of breast	Surgery, radiotherapy	NED (6 years)	
C								
65/M	Gen/+		–	65	Ca of nasopharynx	Chemotherapy, radiotherapy	NED (2.5 years)	Simultaneous appearance

A–patients in which MG preceded cancer. B–patients in which cancer preceded MG. C–co-occurrence of MG with cancer.
Abbreviations: Gen=generalized; Ocu=ocular; Pred=prednisone; Aza=azathioprine; Pex=plasma exchange; Cyclo=cyclosporine; IVIg=intravenous immunoglobulins; Ca=carcinoma; CLL=chronic lymphocytic leukemia; GBM=glioblastoma multiforme; met=metastatic; NED=no evidence of disease.

treated in our institution during the last two decades were studied retrospectively. All patients were treated and followed in our institution, and therefore, complete data as well as pathological confirmation of their tumors were available in their files. Thymomas were searched for by chest CT scans, performed at diagnosis of MG and as part of workup for unexplained worsening of myasthenic symptoms. We examined whether gender, age, generalized disease, seropositivity for acetyl-choline receptor antibodies, occurrence of thymoma, immunosuppressive therapy and occurrence of other autoimmune diseases determined an increased risk for development of extrathymic malignancy. Statistical analysis was performed with the chi-square test.

3. Results

3.1. Clinical features

The study group included 108 women and 80 men in which median age of MG onset was 42 years. There was a typical biphasic age of onset. The younger age group (<45 years) included 100 patients with a clear female predominance (67%). The older age group (>45 years) had a more even gender distribution (male/female=47:41). Seropositivity to acetylcholine receptor (AchR) antibodies was documented in 83% (151/182 patients) and a generalized course of MG was reported in 91% (171/188 patients). In the subgroup with a generalized disease, 85% were seropositive for AchR antibodies. Therefore, this group is representative for the basic epidemiology of MG. The patients were followed up for a mean of 8 years (range 1–45 years). In 44 patients (23.4%), an additional autoimmune disorder was diagnosed. Twenty-eight of them (15%) had an associated thyroid dysfunction. In 21 patients (11%), other autoimmune diseases were reported, as compared to a 5% prevalence of autoimmune diseases in western countries [10]. Four patients had immune thrombocytopenic purpura. Other autoimmune diseases included pemphigus vulgaris (2), psoriasis (2), lichen planus (2), transverse myelitis, crohn disease, ulcerative colitis, scleroderma, vitiligo, pernicious anemia, insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA), alopecia areata, multiple connective tissue disease (MCTD), rheumatic fever (RF), Sjogren's syndrome and systemic lupus erythematosus (SLE).

3.2. Ocurrence of thymoma and extrathymic malignancies in MG

Thymoma was found in 33 (17.6%) patients. Twenty-nine patients (15.4%) developed 30 extrathymic malignant neoplasms (Table 1). Mean age of cancer diagnosis for the entire cohort was 59.2 years, significantly older than for MG. Malignancies were variable and included breast carcinoma (10), colon carcinoma (4), head and neck carcinoma (2), brain tumors (2), other solid tumors (10) and only 2-lymphoproliferative tumors (CLL, Gastric lymphoma). Only 5/29 patients with extrathymic malignancy (17.2%) had an associated thymoma (3 malignant and 2 benign). In the malignant tumors group, 17/29 (58.6%) affected patients were women and 19/29 (65.5%) belonged to the older age group of myasthenia onset (>45 years). Of patients with malignant neoplasm, all except one had generalized myasthenia (96.5%) and 24 (88.8%) were seropositive for anti-AchR antibodies. We examined whether any of these clinical features served as a risk factor for development of malignancy in MG (Table 2). Seropositivity for anti-AchR antibodies, occurrence of thymoma, coincidence of other autoimmune diseases, gender and type of MG did not confer increased risk for cancer. The onset of MG after the age of 45 years was a significant risk factor for the occurrence of cancer.

Tumors were diagnosed between 20 years prior to and 35 years after the diagnosis of MG was made. MG antedated the diagnosis of extrathymic malignancy in 21 patients. Four patients in this group had exacerbation of the MG concurrently with the diagnosis of malignancy. One patient who suffered from hepatocellular carcinoma many years after MG onset was probably infected by HCV after receiving blood transfusion during thymectomy. One patient presented with both diseases simultaneously. In seven patients, malignancy preceded the diagnosis of MG. In one of these patients, diagnosis of MG coincided with the first evidence for metastatic disease.

Finally, we examined whether prior immunosuppressive therapy may have predisposed MG patients to cancer. From our cohort, 102 patients (54%) received any immunosup-

Table 2
Occurrence of extra-thymic cancer in relation to specific clinical features of MG patients

Clinical variable		Incidence of extra-thymic cancer	P value
Gender	Women	17/108 (15.7%)	N.S.
	Men	12/80 (15%)	
Age of onset	<45	10/100 (10%)	$0.02<P<0.05$
	>45	19/88 (21.6%)	
Type of disease	Generalized	28/171 (16.3%)	N.S.
	Ocular	1/17 (5.9%)	
AchR antibody	Seropositive	24/151 (15.9%)	N.S.
	Seronegative	3/31 (9.6%)	
Thymoma	Yes	5/33 (15.1%)	N.S.
	No	24/155 (15.4%)	
Other autoimmune disorder	None	22/144 (15.3%)	N.S.
	Thyroid	5/28 (17.8%)	
	Other	2/21 (9.5%)	
	≥2 additional autoimmune disorder	1/7 (14%)	
Azathioprine therapy	Yes	14/96 (14.6%)	N.S.
	No	15/92 (16.3%)	

N.S.=not significant.

pressive therapy, and 96 of them were treated specifically with azathioprine. The difference in occurrence of cancer in patients who were treated with azathioprine to those who were not treated with azathioprine (or started it after having cancer) was not significant (Table 2).

4. Discussion

Conflicting results on occurrence of cancer in MG patients have been reported in the literature. In some studies, a low risk for cancer (1.7–2.8%) was reported in myasthenic patients [2,4]. In another study, a higher incidence of cancer (7.5%) was found [1], similar to the association of cancer with other autoimmune disorders. In agreement with the latter, we report here that 15.4% of 188 MG patients developed a malignant tumor. It was previously thought that cancer in patients with autoimmune diseases is mostly of hematological origin [6]. In one review of reported cases, the majority of extrathymic malignancies in MG patients were leukemia and reticuloendothelial sarcomas [2]. In our series, most tumors were solid non-hematologic and there was high incidence of breast and colon carcinomas. This is in agreement with previous studies in which cancer types in MG patients had a similar distribution as observed in the general population [1,4]. We did not find increased coincidence of cancer with thymoma. Cancer was diagnosed either before or after MG, spanning 55 years, and the mean age of cancer diagnosis lagged 16 years after mean age of MG. This extremely wide temporal distribution highlights the difficulty in performing studies on the association between MG and cancer and may explain the contradicting findings of previous studies. In a few of our patients, MG was intimately associated with the appearance of malignancy. In five patients, the onset or an exacerbation of MG appeared concurrently with the diagnosis of malignancy. In the patient with renal cell carcinoma (Table 1 no. 4), the first evidence for metastatic disease coincided with the diagnosis of MG, similar to another case report [11]. Our patient with chordoma (no. 6) suffered a significant myasthenic relapse during the year preceding the diagnosis of cancer, after being in stable remission for 6 years. Cross-reacting antibodies to both chordoma and muscle antigens, as described by Carson and Streib [12], may also be related to this case and may indicate a paraneoplastic pathogenic mechanism. However, the lack of a temporal association between cancer and MG in most patients and the lack of relation to specific tumors may suggest that in most cases, MG is not a paraneoplastic phenomenon. Rather, this may indicate a generally increased tendency to develop cancer in MG patients. It has been suggested that primary immune dysregulation may provide the suitable background for both the outburst of autoimmunity (such as in MG) and the reduced immune defense against tumor cells [13]. The occurrence of cancer was similar in patients that were seropositive and seronegative to anti-AchR antibodies. This is in agreement with recent findings of an autoimmune process in most seronegative patients, mediated by anti MuSK [14] and other autoantibodies. In view of the general association between autoimmunity and cancer, we examined whether coincidence of MG with other autoimmune diseases made these patients at an even higher risk for cancer. We did not find higher occurrence of cancer in patients with multiple autoimmune diseases as compared to MG alone.

Our myasthenic patients with cancer were more commonly of the older group and with a generalized disease. Older age is known to carry a higher risk for acquiring cancer, perhaps due to weakness of the immune system. The theory of immune dysregulation, underlying also the association between autoimmunity and cancer, could have further increased the proportion of elderly patients in our series.

Finally, our data shows that azathioprine treatment does not further increase the risk for cancer in MG patients. This is in agreement with long-term follow-up studies of patients with inflammatory bowel disease [15] or after kidney-transplantation [16], indicating that prolonged azathioprine therapy did not increase the risk of cancer. A recent survey in multiple sclerosis patients treated with azathioprine indicated a non-significant absolute increase in risk of cancer [17].

In conclusion, our study shows a high occurrence of extrathymic tumors in myasthenic patients. Given the heterogeneous nature of the study population and wide temporal intervals between MG and cancer, it is very difficult to determine whether their co-occurrence represents a true association. The question remains whether there is a need to perform a periodic search for cancer in the most prevalent sites, especially in the more elderly MG patients with a generalized disease.

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