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Extrathymic Malignancy in Patients with Myasthenia Gravis

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The presence of extrathymic malignancies was investigated in 296 thymectomised myasthenia gravis (MG) cases. In 5 of the 296 cases, extrathymic malignant tumours were observed. 4 of the 5 cases had thymomatous MG. 3 cases had malignant fibrous histiocytoma. Extrathymic malignancies were observed more frequently in thymomatous MG than in non-thymomatous MG. 59 cases (60 tumours), including our 5 cases, who had MG and extrathymic malignant tumours were compiled from the literature. In the 60 extrathymic malignancies, leukaemia and reticulo-endothelial sarcoma were the most frequent types.
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IT IS well known that the incidence of malignant tumours is high in congenitally immunodeficient patients [1]. In autoimmune diseases, malignant tumours of the reticulo-endothelial system and other types of malignant tumours are often observed [2]. Myasthenia gravis (MG) is an autoimmune disease which often shows abnormalities of the thymus. Therefore, the incidence of extrathymic malignancies in MG is an interesting subject. Furthermore, MG is frequently associated with thymoma. MG with thymoma may also be associated with extrathymic malignant tumours at a frequency of 18%, according to one report [3]. Others [4, 5], however, have reported much lower figures ranging from 3% to 8% (see Table 1).

In this study, we report the frequency of extrathymic malignant tumours in thymectomised MG patients and review the literature.

MATERIALS AND METHODS

296 thymectomised Japanese MG patients were investigated. They consisted of 101 males and 195 females. There were 81 cases of thymomatous MG and 215 of non-thymomatous MG. The mean age at onset of MG was 32 years, and its mean duration prior to thymectomy was 3 years and 6 months. The mean postoperative observation time was 8 years (range: 2–25 years). Classification by the MG grade [6], germinal centre formation in the thymus [7], and clinical stage of the thymoma [8] were performed according to the criteria described previously.

RESULTS

An extrathymic tumour was detected in 11 of the 296 cases. 5 were malignant, and 6 were benign. The frequency of extrathymic malignancies in MG was thus 1.7% (5/296). The details of the 5 cases with extrathymic malignancy are summarised in Table 2. The incidence of an extrathymic malignancy in the thymomatous MG cases (4.9%, 4/81) was significantly higher than that in the non-thymomatous MG cases (0.5%, 1/215) ($P < 0.05$). There were no special characteristics in the thymoma histologically or in the germinal centre formation in the thymus in the 4 thymomatous MG patients.

The extrathymic malignant tumour did not develop before the onset of MG in any of the patients. In 2 cases, the malignant tumour was discovered at the same time as the MG was diagnosed. In the 3 other cases, the malignant tumour formed after thymectomy.

DISCUSSION

In the literature, we found 59 MG cases (60 tumours) with an extrathymic malignancy; this includes our 5 cases, but excludes cases with myasthenic symptoms caused by a malignant tumour. The cases treated by Papatestas *et al.* [10] also were excluded because there was no detailed information on the individual cases. The 59 cases consisted of 25 males and 34 females, and 18 thymomatous MG cases and 41 non-thymomatous MG cases.

The primary site of the extrathymic malignancies was the

Table 1. Incidence of extrathymic malignant tumours in MG

Ref.	Total	Rate of thymectomy	Male	Female	Thymomatous MG	Non-thymomatous MG
10	94/1243 (7.6)	18%	31/515 (6.0)	63/728 (8.7)	– (8.9)	– (7.4)
3	11/61 (18.0)	–	–	–	11/61 (18.0)	–
14	21*/381 (5.5)	100%†	5/108 (4.6)	16/273 (5.9)	6/65 (9.2)	15/316 (4.7)
15	6/125 (4.8)	55%	1/34 (2.9)	5/91 (5.5)	3/36 (8.3)	3/89 (3.4)
5	12/432 (3.0)	43%	4/132 (3.0)	9/300 (3.0)	–	–
This study	5/296 (1.7)	100%†	3/101 (3.0)	2/195 (1.0)	4/81 (4.9)	1/215 (0.5)
Total	149/2538 (5.9)		44/890 (4.9)	95/1587 (6.0)	24/243 (9.9)	19/620 (3.1)

Numerators denote patients with a malignant tumour, denominators denote number of patients in each category.
Percentages are shown in parentheses.
* Reported only cases in whom malignant tumours occurred after thymectomy.
† Deals only with thymectomised patients, while we operated on all patients who visited us.

Table 2. Patients with extrathymic malignant tumours

Case (age, sex)	MG grade	Thymoma Hist.	Stage	GC*	Extrathymic tumour Hist.	Interval†	Outcome
1 (42, M)	IIB	None		0	MFH	0	Death due to meningitis
2 (42, F)	11B	Lympho-cytic	III	2	Gastric cancer	6 yr	Alive
3 (54, F)	IIA	Mixed	I	3	MFH	12 yr	MG remission, death due to MFH
4 (55, M)	IIB	Mixed	I	3	Lung cancer	0	Alive, MG stable
5 (33, M)	IIA	Epithelial	III	0	MFH	16 yr	MG remission, death due to MFH

Hist. = histology.
* Germinal centre in uninvolved thymus.
† Interval from onset of MG to diagnosis of extrathymic malignancy.

blood-forming organs (15 cases, leukaemia and sarcoma of the reticulo-endothelial system), breast (8), lung (6), thyroid (5), digestive tract (4), skin (3), uterus (3), malignant histiocytoma (MFH) (3), miscellaneous (8) and unknown (5). Ours were the only cases with MFH.

The time when the extrathymic malignancies were discovered was before the onset of MG (4 cases), at the time MG was diagnosed (12), before the thymectomy (15), after the thymectomy (27) and unknown (2).

An extrathymic malignancy was detected in 5 of 296 MG patients. The frequency of malignancy in Japanese matched for sex, age and follow-up time with our cases was estimated as 3.7/296 persons based on the report of the Research Group for Population-based Cancer Registration in Japan [9]. So, the occurrence of extrathymic malignancy in our cases was almost the same as that in the Japanese normal population.

The 59 cases, including our 5 cases, with MG and extrathymic malignancy found in the literature, consisted of 25 males and 34 females. Since MG is more common in females than males, the slight excess of extrathymic malignancies in females is no surprise. Contrary to Papatestas *et al.*'s report [10], in which breast cancer was the most frequent malignancy in MG patients, tumours of the haematopoietic organs were the most frequent type in the 59 cases. Ours were the only 3 cases of MFH. Since MFH is a recently established concept, it may be forced into other histological groups in the older literature. In our 5 cases with extrathymic malignancy, pathologists re-examined the preparations under a microscope.

Table 1 lists the incidence of extrathymic malignancies in MG patients in studies concerning more than 100 MG patients. The frequency ranged from 1.7% to 7.6%. Papatestas *et al.* [10] reported a high (7.6%) frequency of extrathymic malignancy in MG patients. In their series, only 18% (226 cases) underwent thymectomy. Most of the extrathymic malignancies in their MG cases occurred in non-operated patients or during the period from the onset of MG until thymectomy in operated patients.

The incidence of extrathymic malignancies in MG patients who did not undergo surgical treatment cannot be known from our data, because we operated on all of our MG patients with the intention of undergoing surgery as soon as possible. However, if Papatestas *et al.*'s report is correct, the frequency of extrathymic malignant tumours in MG patients is very high. Oosterhuis' report [5] and our data suggest that thymectomy of MG patients reduces the incidence of extrathymic malignancy.

The reasons why thymectomy reduced the incidence of extrathymic malignancy in MG patients are unclear. However, one reason may be the removal of the abnormal thymus in MG. Several studies in mice show that prior thymectomy reduces the occurrence of leukaemia but not of stomach, skin or mammary tumours induced by carcinogens [11, 12] while it accelerates the growth of tumour grafts [13]. In those reports, oncogenesis was compared in animals with a normal thymus and animals in which a normal thymus was resected. In MG patients, the thymus is not normal. Oncogenesis in patients with an abnormal thymus, such as MG patients, might be different from the above-mentioned results in animals.

Another reason might be the diminished administration of anticholinesterase drugs and/or immunosuppressive drugs due to the good course of MG after thymectomy. The oncogenicity of anticholinesterase drugs is not known, but it is well known that administration of immunosuppressive drugs permits development of a higher frequency of malignant tumours.

The occurrence of extrathymic malignancies in thymomatous MG cases (4.9%, 4/81) was significantly higher than that in non-thymomatous MG cases (0.5%, 1/215). The frequencies of malignancy in Japanese matched for sex, age and follow-up time with our thymomatous MG patients and non-thymomatous MG patients were estimated to be 2.0/81 persons and 1.7/215 persons, respectively, based on [9]. The difference between 2.0/81 vs. 1.7/215 was not statistically significant. Thus, the difference in the frequency of extrathymic malignancies between thymomatous MG cases and non-thymomatous MG cases is not due to the sex, age or follow-up time.

Souadjian *et al.* [3] reported a high frequency (18%) of malignant tumours in thymomatous MG patients. Combined statistical analysis of the data of Papatestas *et al.* [10], Vessey *et al.* [14], Goulon *et al.* [15] and us showed that the occurrence of extrathymic malignancies in thymomatous MG patients was significantly higher than that in non-thymomatous MG patients ($P < 0.05$).

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Phase II Clinical Trial of Doxifluridine in Patients with Advanced Ovarian Cancer

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35 evaluable patients were treated with 5′-deoxy-5-fluorouridine (doxifluridine), a fluoropyrimidine derivative. All patients had been heavily pretreated and had refractory disease. Treatment with doxifluridine at a dosage of 3000 mg/m² given intravenously for 5 successive days at 3-week intervals led to 6 partial remissions (17%). The main side-effects were central neurotoxicity, stomatitis and myelotoxicity, resulting in 2 toxic deaths. In patients with renal function disturbances, toxicity proved to be more severe. We concluded that the drug should not be used in patients with renal impairment. Because responses have been encountered, further evaluation of the drug may be warranted in the less toxic oral form.
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INTRODUCTION

DOXIFLURIDINE (5′-deoxy-5-fluorouridine, 5′-dFUR) is a fluoropyrimidine derivative. Its chemical structure consists of a 5-fluorouracil (FU) molecule attached to a pseudopentose. In animals it has shown marked antineoplastic activity against a wide variety of leukaemias and solid tumours. Activity has been detected after both intraperitoneal [1] and oral administration [2, 3]. It has been established that, compared with other fluoropyrimidines, doxifluridine possesses a higher therapeutic index in animals [1, 2, 4].

Alberto *et al.* [5], who performed a phase I study to evaluate a daily intravenous bolus injection for 5 days, found myelosuppression and stomatitis as dose limiting factors. The maximum tolerated dose was 5000 mg/m²/day [5]. The dose recommended for further clinical use was 4000 mg/m²/day × 5 in patients without previous chemotherapy and 3000 mg/m²/day × 5 in pretreated patients, as has also been reported by others [6, 7].

We selected the drug for phase II testing not only to determine its antitumour activity but also to further characterise its toxic effects. Because the main metabolite of doxifluridine, i.e. 5-fluorouracil, is rapidly converted by the liver and because excretion is independent of renal function, we assumed that no dose adjustments were required for renal function disturbances due to prior treatment with cisplatin. This made the drug attractive for patients with a relapse of ovarian cancer who often have a renal function impairment.

MATERIALS AND METHODS

Protocol entry criteria in this non-randomised study included histologically verified epithelial ovarian cancer stage III or IV (FIGO classification); measurable or evaluable disease and documented disease progression refractory to alkylating drugs and cisplatin. 19 patients reached a partial remission on initial treatment, but showed progression before further tumour

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