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Case Report

Synchronous Multiple Thymoma: Report of Three Cases

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Abstract
We report three cases of synchronous multiple thymoma diagnosed at a single hospital during the 10 years since 1999. Two were accompanied by myasthenia gravis (MG). In two patients, two thymomas were detected by preoperative computed tomography (CT), and in one, a microthymoma was found incidentally on pathologic examination of a resected specimen for gross thymoma and thymus. The multiple lesions were located in the thymus, and extended thymectomy was performed via median sternotomy in all three patients. The World Health Organization subtypes of the multiple thymomas were identical in each patient; however, all were considered to be primary lesions since the larger one was well encapsulated and each tumor was apparently separated. The Masaoka stage was classified as I/I, I/I, and I/II, respectively. Postoperative clinical courses were uneventful and no recurrence was observed in any of the patients. We reviewed 16 reported cases of synchronous multiple thymoma, and discuss the pathogenesis and treatment of this unusual entity.

Key words Multiple thymoma · Synchronous thymoma · Myasthenia gravis · Surgery

Introduction

Multiple thymoma is rare, and until recently was only diagnosed incidentally in the pathologic examination of a surgical specimen. Alifano et al. reviewed 100 patients who underwent limited upper sternotomy during a 10-year period.[1] Thymus surgery represented the most frequent indication (n = 51); however, there were no cases of multiple thymoma. It remains unknown whether so-called synchronous multiple thymoma involves intrathymic dissemination from one primary lesion or multiple primary lesions. To our knowledge, only 13 cases of multiple thymoma have ever been reported.[2] We report three further cases of synchronous multiple thymoma treated in our department between 1999 and 2008.

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Case Reports

Case 1

A 47-year-old woman with ocular type [Myasthenia Gravis Foundation of America (MGFA) class I] myasthenia gravis (MG) concomitant with a possible thymoma was admitted to our department for surgery. The serum level of anti-acetylcholine receptor antibody (AChR Ab) was high, at 3.9 nmol/l (normal level <0.2 nmol/l). Computed tomography (CT) showed an anterior mediastinal mass adjacent to the ascending aorta (Fig. 1-A1). We performed an extended thymectomy via median sternotomy (Fig. 1-A2). The well-encapsulated tumor, which measured 58 × 55 mm, was microscopically diagnosed as type AB thymoma (Fig. 1-A3). Further examination of the thymic tissue apart from the main tumor revealed a tiny and well-encapsulated tumor, 0.5 mm in diameter, which was also diagnosed as type AB thymoma. Postoperative radiotherapy of the whole mediastinum (40 Gy) was performed prophylactically, because the possibility of intrathymic metastasis from the main tumor was not excluded. The patient is alive 9 years after the operation, without any signs of recurrence. Complete remission of MG was achieved.

Case 2

A 40-year-old man was admitted to our department for surgical treatment of two anterior mediastinal tumors

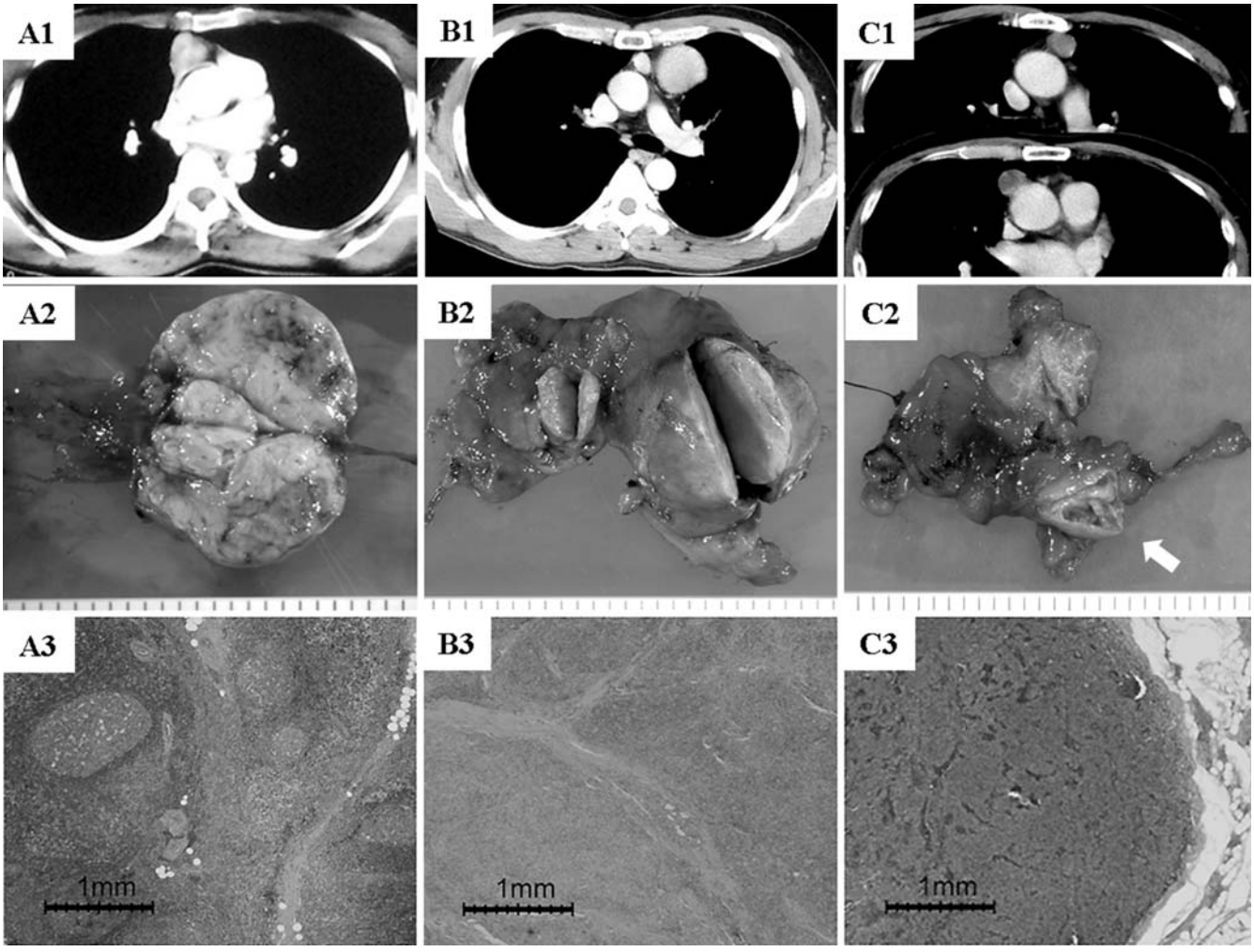

Fig. 1. Computed tomography (CT) findings, gross anatomy, and pathology in the three patients (**A1–3**, **B1–3**, and **C1–3** for cases 1, 2, and 3, respectively). Microscopically, the tumors appeared to be separated, except in case 1 (**A2**, **B2**, and **C2**). In case 3, one tumor was solid and another was cystic (*arrow*) (**C2**). Type AB thymomas were detected in cases 2 and 3 (**A3**, **B3**). Type B1 thymomas were detected in case 3 (**C3**). All except one of the tumors were encapsulated in case 3 (*arrow*)

(Fig. 1-B1). Computed tomography-guided percutaneous needle biopsy of one lesion revealed type AB thymoma. We performed an extended resection of the tumors and thymus (extended thymectomy) via median sternotomy (Fig. 1-B2). The pathological diagnosis of both tumors, which were 60 × 50 mm and 30 × 10 mm, respectively, was type AB thymoma (Fig. 1-B3). The larger tumor was well encapsulated, but the smaller one appeared minimally invasive of the capsule. On gross and microscopic examination these tumors were located in the thymus, but apparently separated. The patient is alive 3 years after the operation, without any signs of recurrence of thymoma.

Case 3

A 70-year-old man presented to our hospital with general lethargy, bilateral eyelid drooping, and a 6-month history of dysphagia. A neurologist diagnosed MG (MGFA class IIIb). The serum AChR Ab level was high, at 160.0 nmol/l, and CT showed two anterior mediastinal masses (Fig. 1-C1). We performed an extended thymectomy (Fig. 1-C2). Pathological examination revealed that both tumors were type B2 thymomas, 30 × 22 mm and 25 × 15 mm in size, respectively (Fig. 1-C3). One tumor was encapsulated, but the other showed minimal invasion. The patient is alive 2 years after the operation without any signs of recurrence of thymoma, with pharmacological remission of MG.

Discussion

Thymoma, which originates from the epithelial cells of the thymus, is the most common tumor of the anterior mediastinum. Multiple thymoma is a well-known entity,

Table 1. Reported cases of multiple thymoma

No.	Age (years)/Sex	No. of tumors	Classification	Maximum diameter (mm)	Stage	MG	First author[Ref.]
1	74/F	2	B1/B1	90/83	I/I	–	Takeuchi[6]
2	37/F	2	B1/B1	55/35	I/I	–	Okada[7]
3	70/M	2	B2/B2	50/24	I/I	–	Okada[7]
4	57/F	2	B1/B1	39/32	I/I	–	Gotoh[8]
5	42/M	2	B1/B2	40/30	I/I	–	Hirai[9]
6	47/M	2	B1/B1	60/25	I/I	+	Ishibashi[10]
7	81/F	2	B1/B1	80/25	I/I	–	Nonami[11]
8	44/M	2	B2/B3	64/60	I/III	–	Yoneda[12]
9	69/M	2	B2/B2	23/2	II/I	+	Mori[13]
10	74/M	3	A/A/A	40/24/10	III/I/I	–	Mori[13]
11	46/M	2	B1/B1	22/15	II/II	+	Mori[13]
12	72/M	3	B1/B2/AB	40/17/12	I/I/I	–	Kawaguchi[2]
13	78/F	2	B1/B1	35/10	I/I	+	Yokota[14]
14	47/F	2	AB/AB	58/0.5	I/I	+	Present case 1
15	40/M	2	AB/AB	60/30	I/I	–	Present case 2
16	70/M	2	B2/B2	30/25	I/II	+	Present case 3

Classification: World Health Organization classification based on the histological findings described in each report. Stage: Masaoka's modified staging
MG, myasthenia gravis

but its incidence is very rare. Maggi et al. reviewed the clinical and histopathological aspects of 241 cases of thymoma, but did not describe multiple thymoma.[3] Bernatz et al. reported 3 (2.2%) out of 138 cases to be multiple thymoma.[4] Jaretzky et al. reported that 1 (6.7%) of 15 patients with thymoma concomitant with MG had two distinct thymomas of different cell types[5] in classical histological differentiation; namely, epithelial, lymphoid, and mixed cells. Since 1971, we have resected 291 thymomas and have encountered only three cases of synchronous multiple thymoma (1.0%). Table 1 summarizes the 16 reported cases we found of synchronous multiple thymoma, including our three.[6–14] The patients ranged in age from 37 to 81 years with a mean age of 59 years, and included 10 men and 6 women. The number of thymomas was two in 14 patients and three in 2 patients. The histological subtypes of the 34 thymomas were type A (n = 3; 8.8%), type B1 (n = 16; 47.1%), type B2 (n = 9; 26.5%), type AB (n = 5; 15.5%), or type B3 (n = 1; 3.1%), and the histological subtypes of the tumors in each individual patient were identical in 13 (81%) and different in 3 (19%).[15] The tumor sizes were similar in each patient, except for patients 9 and 14, in whom there was more than a tenfold difference in diameter among the tumors. Based on Masaoka's clinical staging, 28 lesions were classified as stage I (82.4%), 4 as stage II (11.8%), and 2 as stage III (5.9%). Six of the 16 patients with multiple thymoma had MG (37.5%). Since 15%–54% of thymomas are reportedly associated with MG simultaneously,[16] there seems to be no apparent relationship between MG and synchronous multiple thymoma.

Cases of multiple thymoma may include both intrathymic metastasis and multicentric tumor formation. Hypothetically, multiple centric thymoma may have the following four conditions:

1. When each lesion is diagnosed as stage I, then it is not likely to cause metastasis or dissemination. Of the 16 patients we reviewed, 11 had two or three stage I thymomas, indicative of synchronous multiple thymoma, but in patients 8, 9, 10, 11, and 16, intraspread lesions could not be excluded by this condition.
2. The number of thymomas is usually about two. Only two patients had three lesions and no patient had more than 4 lesions.
3. The size of the thymomas in each patient is relatively similar. Among the patients we reviewed, this was consistent in all except for patients 9 and 14.
4. The histologic types of thymomas in each case are different. This may be the strongest criterion for defining multiple primary lesions, since each histological subtype reflects the original component from which each thymoma originates. Therefore, patients 5, 8, and 12, exhibiting different subtypes of thymomas, were considered as having synchronous multiple thymoma. On the other hand, the possibility of intrathymic metastasis is consistent with the finding that each lesion was of the same histological type in 13 (81.3%) patients.

Inoue et al. reported the difference of loss of heterozygosity (LOH) among identical histological types of thymoma by using a microdissection technique of histo-

logical section or culture of thymoma-epithelial cells.[17] However, it is likely to be difficult to validate LOH in thymoma because there are many lymphocytes surrounding the thymoma cells. Moreover, since hyperplasia of thymic epithelial cells was seen in other thymic tissues, they suggested that the thymus has the potential to develop multicentric neoplasms. In consideration of these conditions, patient 9 might have had intrathymic spread because of a stage II lesion and a smaller stage I lesion, although there is still no clear definition for multiple primary thymoma. Regarding treatment, fewer than 2% of noninvasive thymomas recurred after resection;[17–19] nevertheless, we recommend extended thymectomy for multiple thymoma, since intrathymic spread cannot be excluded.

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