Original Article

Computed tomography imaging characteristics of thymoma: Comparison with and without myasthenia gravis

Hiroyuki Yasui, MD, PhD[1)] ,Soma Kumasaka, MD, PhD[1)] ,
Natsuko Kawatani, MD, PhD[2)] ,Makoto Shibata, MD, PhD[3)] ,Yuka Kumasaka, MD, PhD[1)] ,
Natsumi Katsumata, MD, PhD[1)] ,Yoshito Tsushima, MD, PhD[1)]

[1)] Department of Diagnostic Radiology and Nuclear Medicine, Gunma University Graduate School of Medicine
[2)] Division of General Thoracic Surgery, Integrative Center of General Surgery, Gunma University Hospital
[3)] Department of Neurology, Gunma University Graduate School of Medicine

Abstract

Background: Thymoma is the most common primary neoplasm of the anterior mediastinum. Up to 50% of patients with thymoma have been reported to have myasthenia gravis (MG) , which can be life-threatening. Although some imaging features of thymoma have been reported, data regarding the characteristics of thymoma-associated MG are limited.

Purpose: To determine the computed tomography (CT) imaging characteristics of thymoma through a comparison of patients with and without MG.

Material and Methods: We retrospectively analyzed patients with thymoma (n = 67) who underwent both unenhanced and contrast-enhanced CT before surgery. To compare patients with thymoma with and without MG, we evaluated patients' characteristics and CT features such as tumor shape, tumor edge, presence of calcification, cystic degeneration or necrosis, invasion of mediastinum or lung tissue, longest diameter of the tumor, attenuation value on unenhanced CT, and tumor contrast enhancement (which is calculated by the difference of CT attenuation values before and after contrast enhancement) .

Results: Patients with MG showed lower tumor contrast enhancement (29.8 ± 12.2 vs. 45.9 ± 26.3 Hounsfield units, p = 0.013) compared with patients without MG. No statistical differences were observed in any other factors.

Conclusion: Thymoma with MG was associated with lower tumor contrast enhancement compared with thymoma without MG.

key words thymoma, myasthenia gravis, computed tomography (CT) , tumor contrast enhancement

Corresponding author：Soma Kumasaka, MD, PhD
Department of Diagnostic Radiology and Nuclear Medicine, Gunma University Graduate School of Medicine, Showa-machi 3-39-22, Maebashi, Gunma 371-8511, Japan
Tel: 027-220-8401 Fax: 027-220-8409
Received: 2 December 2022 ／ Accepted after revision: 22 December 2022

INTRODUCTION

Thymoma is an epithelial thymic tumor that represents the most common primary neoplasm of the anterior mediastinum.[1,2] It is well known for some remarkable features, such as an association with myasthenia gravis (MG).[2,3] MG is a neuromuscular junction disease characterized by muscular weakness and fatigability, affecting the ocular, bulbar, and extremity. Because of the involvement of the respiratory muscle, MG can be life-threatening in severe cases.[4] Up to 50% of patients with thymoma have been reported to have MG.[4,5]

The presence of MG affects operative procedures and perioperative risk management.[6] Although guidelines recommend the preoperative measurement of acetylcholine receptor antibodies, 10–15% of patients remain seronegative with standard testing.[7,8] Recently, cell-based assays have been developed to detect antibodies that cannot be detected using routine methods.[9] Because the antigens express on cell membranes and can be clustered and maintain their natural form, cell-based assays have higher sensitivity for detecting the antibody than usual serum tests do. However, these assays are not always performed in all cases.

To select appropriate management strategies in a timely fashion, it is crucial to confirm the presence of MG before performing thymoma surgery. Although some imaging characteristics of thymoma have been reported related to the World Health Organization (WHO) histological grades and staging,[10–13] there have been few studies discussing the different imaging characteristics of thymomas with and without MG.

The aim of our study was to determine computed tomography (CT) imaging characteristics of thymoma through by comparing patients with and without MG.

MATERIALS AND METHODS

Patients

We retrospectively analyzed all patients with thymoma who had undergone surgery at our hospital between March 2009 and July 2021. Inclusion criteria were (1) final diagnosis of thymoma made via pathology,X (2) both unenhanced and contrast-enhanced CT of the chest performed before surgery, and (3) patient age >20 years. Patients without either unenhanced CT or contrast-enhanced CT were excluded from this study.

A total of 87 patients were enrolled in this study. Of these, 20 patients were excluded from further analysis because they did not undergo unenhanced CT (n = 12) or contrast-enhanced CT (n = 8). Therefore, a total of 67 patients (30 males; mean age = 62.7 ± 12.8 years; age range = 33–90 years) were included in the study. Of these, 33 patients were included in previous reports.[14] Fifty-two (77.6%) of the 67 patients were asymptomatic. In these patients, chest radiographs on medical checkup or routine study or chest CT for other diseases helped identify the tumors incidentally. The symptoms in the remaining 15 patients included symptoms of MG such as ptosis and diplopia (7/67, 10.4%), chest pain or discomfort (5/67, 7.5%), shortness of breath (1/67, 1.5%), cough (1/67, 1.5%), and facial swelling (1/67, 1.5%).

After reviewing the surgical records and pathology reports, we identified the tumor types and pathological staging according to the modified Masaoka–Koga staging system and the WHO classification. The diagnosis of MG was made based on a combination of clinical features and one of the following examinations: edrophonium chloride test, serum acetylcholine receptor antibody study, or repetitive nerve stimulation test results.

Based on the presence of MG, we divided

these thymoma patients into two groups: an MG group and non-MG group. The MG group included patients who received a diagnosis of MG preoperatively as well as patients in whom MG appeared during the postoperative follow-up period. Out of 67 patients, 15 patients had MG, comprising 11 with preoperative onset MG and 4 with postoperative onset MG.

Age, sex, body mass index (BMI), and symptoms were recorded for all patients. Summary of patients' characteristics are shown in Table 1.

The institutional review board approved all aspects of this study. Considering the study's retrospective nature, informed consent was obtained using the opt-out method on our hospital website.

CT protocol

Unenhanced and contrast-enhanced CT was performed for all patients with a tube voltage of 120 kVp before surgery using a multidetector CT (Aquilion ONE; Toshiba, Tokyo, Japan; Aquilion 64; Toshiba, Tokyo, Japan; Lightspeed VCT; GE Medical Systems, Waukesha, WI, USA; Revolution HD, GE Healthcare, Milwaukee, Wisconsin, USA; and SOMATOM Definition Flash; Siemens Healthcare, Forchheim, Germany). After unenhanced CT, iodinated contrast media (Iopamiron; Bayer Yakuhin,

Table 1. Summary of Patients' Characteristics

		With MG (%) n = 15	Without MG (%) n = 52
Age (years)		55.9 ± 15.7	64.6 ± 11.2
Sex			
	Male	6 (40.0)	24 (46.2)
	Female	9 (60.0)	28 (53.8)
BMI		24.8 ± 5.4	23.2 ± 4.0
Masaoka–Koga staging			
	Ⅰ	3 (20.0)	15 (28.8)
	Ⅱ	9 (60.0)	30 (57.7)
	Ⅲ	2 (13.3)	7 (13.5)
	Ⅳa	1 (6.7)	0
WHO pathologic classification			
	A	1 (6.7)	8 (15.4)
	AB	3 (20.0)	17 (32.7)
	B1	2 (13.3)	7 (13.5)
	B2	3 (20.0)	10 (19.2)
	B3	6 (40.0)	7 (13.5)
	MNT	0	3 (5.8)

Abbreviations: BMI, body mass index; MG, myasthenia gravis; MNT, micronodular thymoma with lymphoid stroma; WHO, World Health Organization.
Values are given as n or mean ± SD.

Osaka, Japan; 350 mgI/mL, 600 mgI/kg patient weight) was administered intravenously, and postcontrast images were acquired in the portal venous phase using a scan delay of 60–70 seconds. Axial and coronal images at 5-mm thickness were used for the following image analysis.

Image analysis

Two diagnostic radiologists with 3 and 10 years of experience in CT interpretation separately reviewed all CT images on a PACS workstation in randomized order. The radiologists were aware that the patients had thymomas but did not know the presence or absence of MG.

The collected qualitative data were the shape of the tumor (classified as round if the long- to short- axis ratio <1.5, round/other), tumor edge (classified as smooth if the entire contour is smooth, smooth/rough), presence of calcification (with/without), cystic degeneration or necrosis (presence of focal areas of low attenuation in the tumor, with/without), and invasion of mediastinum or lung tissue (yes/no). The collected quantitative data were longest diameter of the tumor (observed in the axial and coronal, with the longest lesion diameter noted), attenuation value on unenhanced CT, and tumor contrast enhancement (which is calculated by the difference of CT attenuation values before and after contrast enhancement). To measure the attenuation value, the region of interest (ROI) was manually drawn at the level where the tumor appeared largest on the cross-sectional image. Peripheral areas, calcifications, cystic or necrotic components, and beam-hardening artifacts were excluded from the ROIs.

In cases of discrepancies in qualitative data between the two radiologists, consensus was reached to determine the imaging data. For quantitative data, if the difference between the results of the two measurements was <10%, the average value was used for further analysis. If the difference was ≥10%, the two radiologists remeasured the values together.

Statistical analysis

We performed the Mann–Whitney *U* test to compare continuous data and chi-square test (Yates' chi-square test and Fisher's exact test) to compare the categorical data between the two groups. All tests were two-sided, and *p* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS Statistics 28; IBM Japan, Tokyo, Japan).

RESULTS

Patients with MG showed lower tumor contrast enhancement (29.8 ± 12.2 vs. 45.9 ± 26.3 Hounsfield units [HU], $p = 0.013$) as compared with patients without MG (**Figures 1–3**). Although there was a tendency towards higher rate of invasion (33.3% vs. 11.5%) and slightly longer diameter of the tumor (62.6 ± 30.5 vs. 54.6 ± 26.8 mm) in patients with MG group, the difference was not significant. No significant

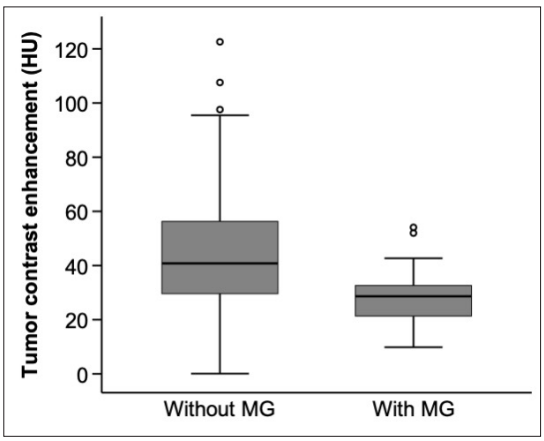

Fig. 1 Box plot of tumor contrast enhancement for patients with thymoma with and without MG. Tumor contrast enhancement was significantly lower in patients with MG than in those without MG ($p = 0.013$).

differences in any other factors were apparent between the two groups (Table 2).

DISCUSSION

This study investigated the CT imaging characteristics of thymoma by comparing patients with and without MG. We showed that contrast enhancement of thymoma was significantly lower in patients with MG compared to those without MG. Since 10–15% of patients remain seronegative with standard acetylcholine receptor antibodies testing, the results of the current study may assist in determining whether to apply an additional cell-based assay in patient with thymoma who are negative for acetylcholine receptor antibodies.

To design appropriate treatment strategies in a timely fashion, preoperative tumor staging and classification based on imaging characteristics are important. Although several studies have investigated the staging and classification of thymoma using preoperative imaging modalities such as CT, magnetic resonance imaging, and positron emission tomography, data regarding the characteristics of thymoma-associated MG (T-MG) are limited.[10,15]

Some patients with thymoma can develop MG after thymectomy, even though they have no history of MG or associated symptoms. Previous studies have reported that MG

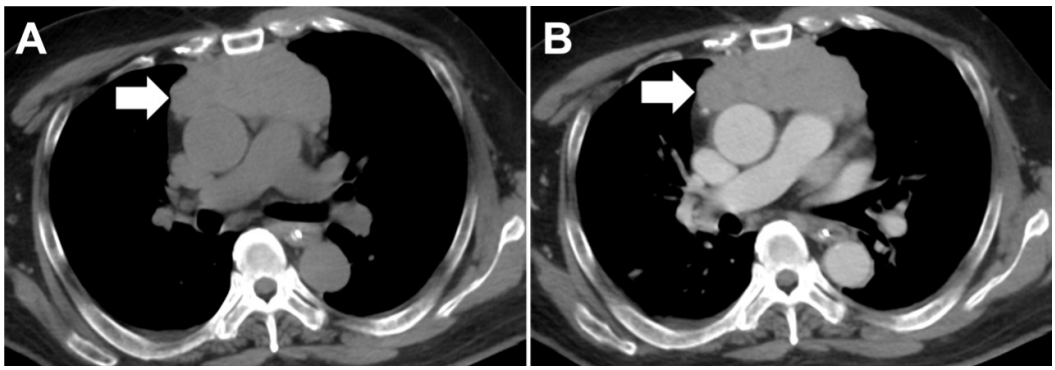

Fig. 2 A male patient in his 50 s with thymoma (WHO type B3) with MG. Axial (a) unenhanced CT and (b) contrast-enhanced CT showing lower tumor contrast enhancement (17.8 HU) (arrows).

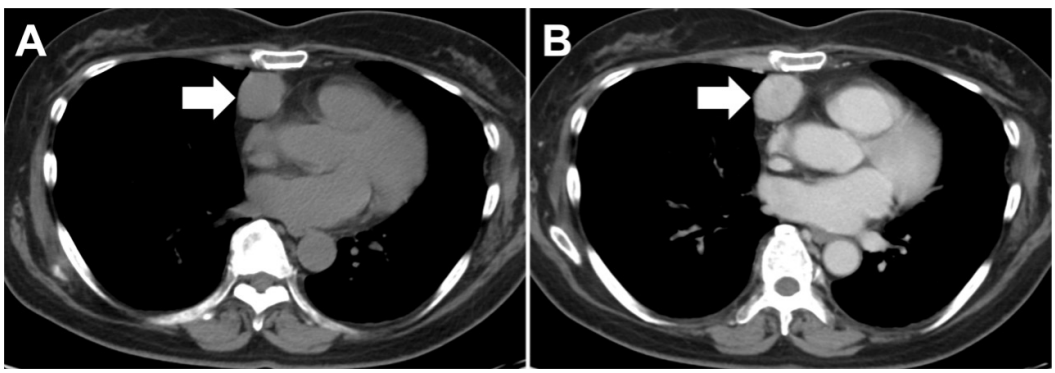

Fig. 3 A female patient in her 50 s with thymoma (WHO type A) without MG. Axial (a) unenhanced CT and (b) contrast-enhanced CT showing higher tumor contrast enhancement (95.5 HU) (arrows).

developed in 1.5–28% of thymoma cases after total thymectomy,[16] which is consistent with the proportion found in our study (7.1%, 4/56) .

In our study, contrast enhancement of thymoma was significantly lower in patients with MG compared with those without MG, possibly reflecting pathological differences. Previous studies reported that T-MG was more common in patients with cortical thymoma (WHO type B) .[17–19] In fact, in our study, type B was more commonly observed in the MG group (73.3%, 11/15) compared with the non-MG group (46.2%, 24/52) . Furthermore, it was reported that type B thymoma might have lower enhancement, compared with that of type A.[20] This might be due to a lower extracellular volume fraction of type B thymoma.[21] However, since we used the portal venous phase as postcontrast images in our study, further studies with equilibrium phase may be needed to confirm this hypothesis.

Regarding other results of CT imaging features of thymoma, we found a tendency towards higher rate of invasion and longer diameter of the tumor without significant differences. This may also be due to higher proportion of type B in the MG group, as type B thymoma has been reported to tend to exhibit a

Table 2. Imaging features of thymoma patients with and without MG

		With MG (%) n = 15	Without MG (%) n = 52	*p* value
Tumor shape				1.000
	Round	5 (33.3)	17 (32.7)	
	Other	10 (66.7)	35 (67.3)	
Tumor edge				0.154
	Smooth	6 (40.0)	32 (61.5)	
	Rough	9 (60.0)	20 (38.5)	
Presence of calcification				0.327
	Yes	5 (33.3)	11 (21.2)	
	No	10 (66.7)	41 (78.8)	
Cystic degeneration or necrosis				0.771
	Yes	8 (53.3)	24 (41.2)	
	No	7 (46.7)	28 (53.8)	
Invasion of mediastinum or lung tissue				0.106
	Yes	5 (33.3)	6 (11.5)	
	No	10 (66.7)	46 (88.5)	
Longest diameter of the tumor (mm)		62.6 ± 30.5	54.6 ± 26.8	0.340
Attenuation value on unenhanced CT (HU)		42.2 ± 9.8	41.6 ± 13.0	0.741
Tumor contrast enhancement (HU)		29.8 ± 12.2	45.9 ± 26.3	0.013

Abbreviations: CT, computed tomography; HU, Hounsfield units; MG, myasthenia gravis.
Values are given as n or mean ± SD.

larger size and infiltration of surrounding stractures.[10]

The present study had some limitations. First, the study was retrospective and included only patients who underwent surgical resection; thus, selection bias was unavoidable. Second, the sample size of the study was small (n = 67), especially for T-MG cases (n = 15). Because the small sample size may lead to limited statistical power, the evidence was limited regarding the use of a specific number of tumor enhancements in this study as a cutoff value for a prediction of MG.

CONCLUSION

Patients with thymoma with MG had lower tumor contrast enhancement compared with those without MG. To determine the specific cutoff value for predicting T-MG, further studies with larger sample sizes are needed.

References

1. Detterbeck FC, Zeeshan A. Thymoma: Current diagnosis and treatment. Chin Med J (Engl). 2013;126:2186–91. doi: 10.3760/cma.j.issn.0366-6999.20130177.
2. Shelly S, Agmon-Levin N, Altman A, et al. Thymoma and autoimmunity. Cell Mol Immunol. Nature Publishing Group; 2011;8:199–202. doi: 10.1038/cmi.2010.74.
3. Romi F. Thymoma in myasthenia gravis: From diagnosis to treatment. Autoimmune Dis. 2011;1. doi: 10.4061/2011/474512.
4. Romi F, Hong Y, Gilhus NE. Pathophysiology and immunological profile of myasthenia gravis and its subgroups. Curr Opin Immunol. Elsevier Ltd; 2017;49:9–13. doi: 10.1016/j.coi.2017.07.006.
5. Kumar R. Myasthenia gravis and thymic neoplasms: A brief review. World J Clin Cases. 2015;3:980. doi: 10.12998/wjcc.v3.i12.980.
6. Nabe Y, Hashimoto T, Tanaka K, et al. Relationship between anti-acetylcholine receptor antibodies and the development of post-thymectomy myasthenia gravis in patients with thymoma: a single-center experience. Gland Surg. 2021;10:2408–13. doi: 10.21037/gs-21-287.
7. Gilhus NE. Myasthenia Gravis. Longo DL, editor. N Engl J Med. 2016;375:2570–81. doi: 10.1056/NEJMra1602678.
8. Cata JP, Lasala JD, Williams W, et al. Myasthenia Gravis and Thymoma Surgery: A Clinical Update for the Cardiothoracic Anesthesiologist. J Cardiothorac Vasc Anesth. Elsevier Inc.; 2019;33:2537–45. doi: 10.1053/j.jvca.2018.07.036.
9. Rodriguez Cruz PM, Huda S, López-Ruiz P, et al. Use of cell-based assays in myasthenia gravis and other antibody-mediated diseases. Exp Neurol. Elsevier Inc.; 2015;270:66–71. doi: 10.1016/j.expneurol.2015.01.011.
10. Han X, Gao W, Chen Y, et al. Relationship Between Computed Tomography Imaging Features and Clinical Characteristics, Masaoka–Koga Stages, and World Health Organization Histological Classifications of Thymoma. Front Oncol. 2019;9:1–13. doi: 10.3389/fonc.2019.01041.
11. Yamazaki M, Oyanagi K, Umezu H, et al. Quantitative 3D shape analysis of CT images of thymoma: A comparison with histological types. Am J Roentgenol. 2020;214:341–7. doi: 10.2214/AJR.19.21844.
12. Sadohara J, Fujimoto K, Müller NL, et al.

Thymic epithelial tumors: Comparison of CT and MR imaging findings of low-risk thymomas, high-risk thymomas, and thymic carcinomas. Eur J Radiol. 2006;60:70–9. doi: 10.1016/j.ejrad.2006.05.003.
13. Benveniste MFK, Rosado-de-Christenson ML, Sabloff BS, et al. Role of imaging in the diagnosis, staging, and treatment of thymoma. Radiographics. 2011;31:1847–61. doi: 10.1148/rg.317115505.
14. Yajima T, Mogi A, Shimizu K, et al. Quantitative analysis of metabolic parameters at 18F–fluorodeoxyglucose positron emission tomography in predicting malignant potential of anterior mediastinal tumors. Oncol Lett. 2020;19:1865–71. doi: 10.3892/ol.2020.11276.
15. Iannarelli A, Sacconi B, Tomei F, et al. Analysis of CT features and quantitative texture analysis in patients with thymic tumors: correlation with grading and staging. Radiol Medica. Springer Milan; 2018;123:345–50. doi: 10.1007/s11547-017-0845-4.
16. Kondo K, Monden Y. Myasthenia gravis appearing after thymectomy for thymoma. Eur J Cardio-thoracic Surg. 2005;28:22–5. doi: 10.1016/j.ejcts.2005.03.039.
17. Marx A, Ströbel P, Weis C-A. The pathology of the thymus in myasthenia gravis. Mediastinum. 2018;2:66–66. doi: 10.21037/med.2018.12.04.
18. Vaideeswar P, Padmanabhan A, Desphande JR, et al. Thymoma: A pathological study of 50 cases. J Postgrad Med. 2004;50:94–7.
19. Yu L, Zhang XJ, Ma S, Jing Y, et al. Different characteristics of thymomas with and without myasthenia gravis. Ann Surg Oncol. 2012;19:94–8. doi: 10.1245/s10434-011-1896-8.
20. Tomiyama N, Johkoh T, Mihara N, et al. Using the World Health Organization classification of thymic epithelial neoplasms to describe CT findings. Am J Roentgenol. 2002;179:881–6. doi: 10.2214/ajr.179.4.1790881.
21. Chang CC, Lin CY, Chu CY, et al. Extracellular volume fraction measurement correlates with lymphocyte abundance in thymic epithelial tumors. Cancer Imaging. Cancer Imaging; 2020;20:71. doi: 10.1186/s40644-020-00349-4.