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Thymolipoma and its Association with Myasthenia Gravis: a Multi-center Experience

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ABSTRACT

Background: Thymolipoma is a rare benign thymic tumor that arises in the anterior mediastinum. It presents with non-specific symptoms such as chest pain and dyspnea due to compression of the tumor on surrounding structures. In addition, this tumor is associated with paraneoplastic syndromes, including myasthenia gravis. Such a relationship is still not understood and requires investigation. **Objective:** Investigate the significance of myasthenia gravis in thymolipoma patients. **Methods:** We present a series of 16 thymolipoma cases from multiple medical centers. Data extraction included demographic, diagnostic, radiological and laboratory, and clinical outcome variables. We also used the modified Osserman score to assess the severity of myasthenia gravis. **Results:** Ten patients were males, and six were females; the sample mean age was 39.9 years (SD = 16.7). Upon presentation, 7/16 patients were asymptomatic, 4/16 patients had chest pain, and 2/16 had dyspnea. Seven patients were having myasthenia gravis; they experience generalized weakness (3/7), diplopia (2/7), ptosis (1/7), and bulbar weakness (1/7). Serum acetylcholine receptor antibody (AChRAb) was positive in 4 patients. All patients underwent thymectomy either via sternotomy or thoracotomy. After proper follow-up, only 2/7 of myasthenic patients had a complete remission of symptoms, no tumor recurrence was observed. **Conclusion:** Although the effect of using steroids in myasthenic patients on thymolipomic transformation still needs confirmation, diagnosis of thymolipoma should be kept in mind in myasthenic patients presenting with relevant symptoms and taking steroids. Furthermore, complete remission of myasthenic symptoms after removal of thymolipoma needs further investigation.

Keywords: Thymolipoma, Myasthenia gravis, Thymus Neoplasms, Steroids, Surgical resection.

1. BACKGROUND

Thymolipoma is a rare mediastinal mass that constitutes less than 10% of thymic tumors. This encapsulated tumor is benign, slow-growing, and does not recur after complete surgical resection. It has an incidence of approximately 0.12 per 100,000 persons each year (1, 2). It was first described as a simple thymic lipoma in 1916 (3), but then it was distinguished as "thymolipoma" by Hall in 1948 (4). This tumor presents in the anterior mediastinum, with vague symptoms like dyspnea, chest pain, and fatigue; it also presents with paraneoplastic syndromes such as Graves' disease, pure red blood cell aplasia, aplastic anemia, hypogammaglobulinemia, Hodgkin's disease, and myasthenia gravis (5). These syndromes make thymolipoma of clinical importance, especially with the lack of studies on this rare tumor. Furthermore, symptoms of myasthenia gravis were relieved after surgical resection of thymolipoma, which puts this association under the spotlight and makes it in need of explanation (1). In this descriptive retrospective study, we collected clinical data from multiple centers in Jordan. These data include laboratory results, clinical manifestations, and radiological findings.

2. OBJECTIVE

The aim of the study was to investigate the significance of myasthenia gravis in thymolipoma patients.

3. MATERIAL AND METHODS

Patients and Study design

ID	Age (y)	Sex	Presenting symptoms	Comorbidities	Type of MG	MG Severity
Case #1	27	M	Asymptomatic	-	-	-
Case #2	29	M	Ptosis, diplopia, headache	MG	Ocular	Class I
Case #3	6	F	Asymptomatic	Asthma	-	-
Case #4	56	F	Generalized weakness, diplopia	MG, HTN	Ocular	Class I
Case #5	48	M	Generalized weakness, bulbar	MG	Bulbar	Class III
Case #6	26	M	Asymptomatic	-	-	-
Case #7	32	M	Asymptomatic	-	-	-
Case #8	47	M	Progressive generalized weakness	MG, Hyperparathyroidism	Generalized	Class II
Case #9	51	M	Asymptomatic	MG, Lung Fibrosis, ß-thalassemia	Generalized	Class IIIa
Case #10	31	M	Asymptomatic	MG	Generalized	Class I
Case #11	17	F	Asymptomatic	MG	Generalized	Class III
Case #12	47	F	Chest pain	HTN, DM, IHD	-	-
Case #13	72	F	Chest pain, dyspnea	DM, HTN, IHD, interstitial pulmonary disease, pulmonary HTN	-	-
Case #14	61	M	Chest pain	HTN, IHD, Crohn's Disease	-	-
Case #15	52	M	Chest pain, dyspnea	HTN, IHD	-	-
Case #16	36	F	Chest infection, high fever	-	-	-

Table 1. Patients' characteristics

This study addresses 16 patients from tertiary medical centers in Jordan. Centers including King Abdullah University Hospital (KAUH), King Hussein Cancer Center (KHCC), Jordan University Hospital, and the Royal Medical Services (RMS).

Data from medical records were extracted retrospectively from June 2002 to June 2021. A standardized Excel sheet was used for data collection. Variables included demographics like age, sex, and institution, presenting symptoms, comorbidities, patient diagnostics including computer tomography (CT) notes and serum acetylcholine receptor antibody (AChRAb) levels, type of myasthenia gravis and its severity, administered drugs, surgical approach, remission status of myasthenia, and follow-up period. An ethical approval was granted from the institutional review board (IRB) affiliated to our institute (IRB no. 2021/179).

Screening and Management

The diagnosis of thymolipoma was based on the CT of the chest. All patients were screened for AChRAb. A modified Osserman classification score was used to assess the severity of myasthenia gravis (6). Our patients were treated surgically using one of the following procedures: (1) Full median sternotomy with extended thymectomy. It includes resection of the thymus and the thymolipoma with the anterior mediastinal fat between phrenic nerves and pleurae, the pericardium, and the diaphragm. In patients with myasthenia gravis, more extensive surgery has been performed, including the right and left pericardiophrenic angles, the aortopulmonary window, the aortocaval groove, and retroinnominate space, and the perithyroid area (2). Anterolateral thoracotomy with standard thymectomy, including the thymolipoma. The chest cavity is accessed through the 5th intercostal space (3). Right-sided video-assisted thoracoscopic extended thymectomy using three ports (2 in the 5th intercostal space in the mid-and anterior axillary lines and 1 in the 3rd intercostal space, mid axillary line). Resection of the entire anterior mediastinal content between the sternum, pericardium, diaphragm, pleurae, and phrenic nerves, including thymus and thymolipo-

ID	Age	Sex	CT Notes	Tumor weight (g)	Dimensions (cm)	Serum AchRAb	Lymphocytes	WBCs
Case #1	27	M		2700	34 × 23 × 9	-	0.118	11.3
Case #2	29	M	1.5 cm soft tissue lesion in the anterior mediastinum	150	18 × 5 × 1.5	+	0.112	20
Case #3	6	F	Large soft lesion with mixed soft tissue and fat component occupying most of the right hemithorax	1100	28 × 12 × 6	-	0.663	17.1
Case #4	56	F	8 × 7 cm Mediastinal mass	120	7 × 5 × 1	+	0.38	13.2
Case #5	48	M	20 × 215 cm Huge Mediastinal Mass	400	17 × 19 × 1	+	0.22	11.4
Case #6	26	M	5 × 3 cm Mediastinal Mass	100	7 × 4 × 1	-	0.29	7.8
Case #7	32	M	10×20 cm Mediastinal Mass	350	20 × 13 × 1	-	0.34	10.1
Case #8	47	M	Aortopulmonary mass	62	9 × 7.5 × 2	+	0.21	9.7
Case #9	51	M	2 × 4 well defined lesion in the anterior mediastinum	156	2 × 4	+	0.31	Leukocytosis 16.5
Case #10	31	M	None	58.5	10.5 × 6.5 × 2	+	0.21	10.1
Case #11	17	F	No evidence of mediastinal mass lesion	11	8 × 7 × 1	+	0.35	13.4

Table 2. Diagnostic procedures and tumor characteristics. AChRAb: Acetylcholine receptor antibody.

ma. Most of the dissection was performed using an energy device.

Data analysis

Tables were employed to summarize individual patient data. Summar statistics were used, such as medians for continuous variables and frequencies or percentages for categorical data. A scatter plot was generated using the "ggplot2" package in R software (version 4.0.5) (7, 8).

4. RESULTS

We reviewed 16 cases diagnosed with thymolipoma. The mean age was 39.9 years (SD = 16.7), and patients' ages ranged from 6 to 72 years. Ten patients were males, and six patients were females. When presented, 7/16 patients were asymptomatic. Four patients suffered from compression symptoms such as chest pain (4/16) and dyspnea (2/16). Moreover, other four patients experienced myasthenic symptoms, including generalized weakness (3/16), diplopia (2/16), ptosis (1/16), and bulbar weakness (1/16). Case #2 had a headache in addition to his ptosis and diplopia. Furthermore, case #16 had a chest infection with a high fever. Comorbidities were hypertension in 5 patients, ischemic heart disease in 4 patients. Case #13 had both in addition to diabetes mellitus. Case #3 had asthma, and Case #8 had hyperparathyroidism. Case #9 had lung fibrosis in addition to ß-thalassemia. Case #14 had Crohn's disease. Patients' characteristics are summarized in Table 1.

Seven patients out of 16 had myasthenia gravis; 3 of them were asymptomatic upon presentation. Type of myasthenia gravis was generalized in 4 patients, ocular in 2 patients, and bulbar in one patient. As for severity, Osserman classification score revealed that patients with generalized myasthenia gravis were classified as I and II, one patient in each class, and two patients were classified as III and IIIa, respectively. Patients with an

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Table 3. Patient management and follow-up. NMBs: Neuromuscular blockers, VAT: Video-assisted Thoracotomy.

ocular type were in class I. Furthermore, one patient with a bulbar type had a class III disease.

For most patients, mediastinal masses of variable sizes were found in CT images (Figure 1 a, b) or were sometimes reported as "soft lesions", case #8 was reported to show an aortopulmonary mass. For detection of myasthenia gravis, serum AChRAb was positive in all seven myasthenic patients. Two patients were investigated by electromyography nerve stimulation (Table 2). Among seven patients with myasthenia gravis, 3/7 patients were on a neuromuscular blocker (pyridostigmine), and all of them were treated with corticosteroids to relieve myasthenic symptoms (Table 3). As for the primary treatment, all patients underwent thymectomy either through sternotomy, thoracotomy, or video-assisted thoracoscopic surgery. No postoperative complications were observed, except for case #2, who experienced chylothorax. After excision, tumor weights ranged from 220 to 2900 gm, with most tumors weighing less than 500 gm. Lesions were weighing above 1000 gm in 3 non-myasthenic patients (Figure 2 a, b). None of the patients experienced recurrence. Although only 2/7 patients had a complete remission of myasthenia gravis, they were followed up for 192 and 48 months, respectively. Images of some resected tumors are shown in Figure 3.

5. DISCUSSION

Thymolipoma is also known as lipoma of the thymus, benign thymoma, thymolipomatous hamartoma, lipothymoma, and mediastinal lipoma (9, 10). Moran et al. conducted a clinicopathological review that contained 33 cases and studied the radiological and histopathological aspects of thymolipoma in their sample (11). In another report of 9 patients, some patients had myasthenia gravis, and their symptoms were relieved after resection of the mass, which emphasizes this association.

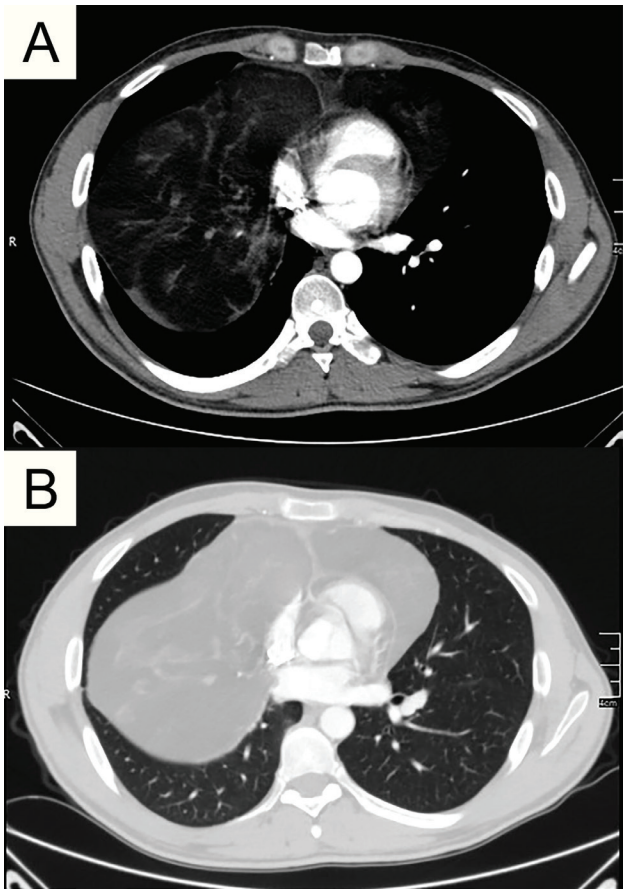

Figure 1. CT images for Case #1 from the (A) mediastinal window and the (B) pulmonary window

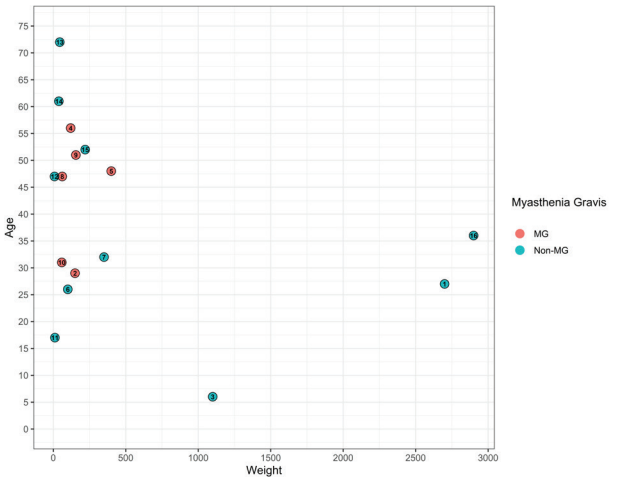

Figure 2. Demonstration of tumor weight for myasthenic and non-myasthenic patients across different ages. MG: Myasthenia gravis

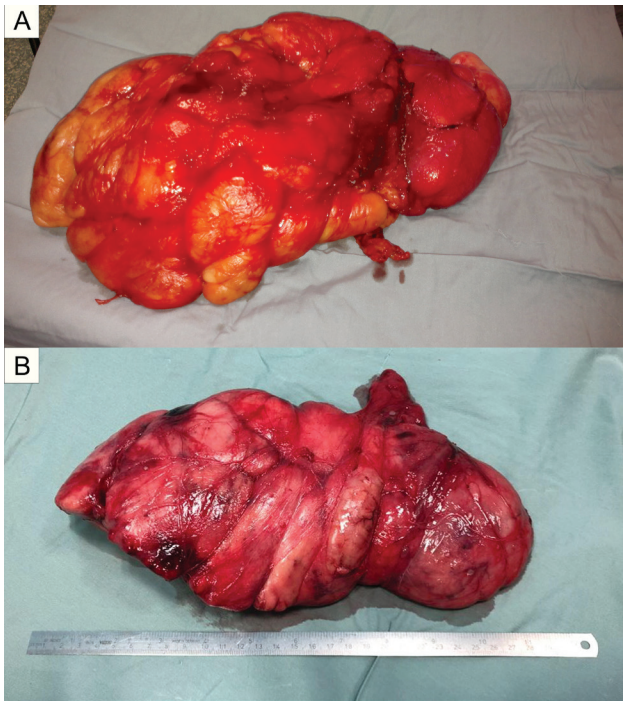

Figure 3. Resected tumors for (A) Case #1 weighing 2700 gm and (B) Case #3 weighing 1100 gm

Furthermore, none of their patients experienced tumor recurrence (12). In 2014, Huang et al. made a vital comparison between thymomatous and non-thymomatous myasthenia gravis and their outcomes after surgical treatment, 12 of these patients had thymolipoma, and their mean duration of myasthenic symptoms was the greatest before the surgery among other groups of the study ($p < 0.001$) (13).

The pathogenesis of thymolipoma is still unclear, but it has been thought to follow one of two theories, the hyperplasia theory, which suggests defining the tumor as a lipoma of thymic fat and the mixed tumor theory that defines thymolipoma as a mixture of mesenchymal and endodermal neoplasm (14, 15). A cytogenetic analysis allowed a more accurate characterization of these lesions that carry varying amounts of mature thymic and adipose tissue. Also, it can demonstrate individual cases' pathogenesis (16, 17). The first cytogenetic study of a thymolipoma was reported by Hull et al. in 1995, describing it as a proliferating thymolipoma due to the presence of adipose and abnormal thymic tissue (16). Another study done in 2009 used cytogenetic analysis to figure out the exact pathogenesis of their case, which was a neoplasm of thymic fat (17).

It is challenging to diagnose thymolipoma according to clinical symptoms or signs, and biopsy is the definitive diagnostic tool (18). However, up to 50% of thymolipoma patients remain asymptomatic, with the tumor getting bigger without invading surrounding structures until it is incidentally discovered in radiographic images (19). The other half of patients mainly present with cough, dyspnea, chest pain, hoarseness, and upper respiratory tract infection (20). These findings are consistent with ours, as almost half of our patients (7/16) were asymptomatic at presentation. Damadoglu et al. reported their experience of 10 cases and found fatigue to be the most prominent symptom among their cohort (1). Generally, when thymolipoma is symptomatic, respiratory symptoms predominate.

A plethora of studies have suggested a relationship between myasthenia gravis and thymolipoma (1, 21-23). As an autoimmune disease, myasthenia gravis is associated with antibodies directed against the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and therefore characterized by muscle weakness and fatigue

(24). The exact pathogenesis of this association is unclear, but some genetic findings revealed the presence of myoid cells, which might play a role as a stimulus to the autoimmune response in myasthenia gravis patients (1). In addition, therapies include steroids, which might hasten the effect of fatty degeneration in thymomas and enhance their shift into thymolipomas (13). Seven of our patients had myasthenia gravis; four of them were on steroids. The prevalence of myasthenia gravis associated with thymolipoma in our cohort was (43.8%) which supports the results reported by Damadoglu et al. and Rieker et al. (1, 12).

It was reported that thymolipoma occurs most frequently in patients aged 2 to 67 years, without sex predilection. A retrospective study of 27 patients found that the mean age of presentation is 26.7 years, with most patients presenting in the first four decades of life (10). Another case series found that ages range between 16 and 67 years with a mean age of 34.1 years (1). As to myasthenia gravis patients, Pan et al. found thymolipoma to appear in older age groups and have a lower mean weight of the tumor compared to non-myasthenic patients (3). Since myasthenic patients get diagnosed earlier, as soon as their symptoms manifest, the same phenomenon was observed in our cohort of patients as described in Figure 1. In the present report, the mean age was 39.9 years, higher than the previously published studies. The mean weight of thymic tissue removed was 136.8 g in myasthenic patients and 614.2 g in non-myasthenic patients.

About 85% of generalized myasthenia gravis patients have autoantibodies against post-synaptic acetylcholine receptors (AChRAb) (25), the other 15% are described as having seronegative myasthenia gravis (SNMG), and about 45% of them have anti-MuSK-Abs (26). Respiratory failure, diffuse limb weakness, bulbar weakness, and intermittent ptosis suggest the diagnosis of myasthenia gravis associated with elevated serum AChRAb. Three out of seven of our myasthenic patients presented with generalized weakness, and their serology results showed an elevation in AChRAb titers. Although the use of preoperative AChRAb titers to predict the prognosis and severity of symptoms has not been well-documented, it is still a promising predictor that might be useful to discriminate between ocular and generalized types of myasthenia gravis (27).

The optimal treatment for thymolipoma is thymectomy using open surgical techniques like sternotomy or thoracotomy and minimally invasive techniques using video-assisted thoracoscopic surgery or robotic surgery. After complete resection, thymolipoma has a good prognosis with no malignant transformation or recurrence (20). Regarding the surgical outcomes in myasthenic patients, total resection might aid in improving their symptoms (28), as two out of seven among our MG cases exhibited remission. Case #2 had ocular myasthenia gravis, an extremely rare association, and his surgical outcomes are supported by a case report published by Mardi et al. of a patient with ocular myasthenia gravis associated with thymolipoma and their symptoms improved after the operation (28). Huang et al. looked at post-operative results of thymectomy in thymolipomatous, thymomatous, and non-thymomatous myasthenic patients and found the rate of stable remission to be significantly higher in the thymolipomatous group than thymomatous group (41.7% vs. 28.8%, p = 0.029). However, no reliable conclusion can be achieved yet. As for long-term effects, total resection potentially compromises future immunological competence. Thus, the immunological milieu should be monitored, especially in young patients (29, 30).

6. CONCLUSION

Our study reports a 19-year multicenter experience. To our knowledge, it is one of the largest cohorts of thymolipoma associated with myasthenia gravis. Although it bears some limitations, including the retrospective nature of data collection, especially data collected a long time ago, the small sample size raises some difficulties in the statistical analysis. In addition, a lack of symptoms of thymolipoma results in difficulty in diagnosing the pathology, which leads to underreporting. Therefore, we recommend conducting more research to understand the etiology of thymolipoma and the effect of surgical resection of thymolipoma on myasthenic symptoms to determine the subcategory of patients who can benefit from this modality.

- **Declaration of patient consent**: A waiver of patients' consents was approved from the IRB due to the retrospective nature of data collection.
- **Author's Contribution**: SH: Conceptualization, Project Administration, Data Collection, Data Analysis, Draft Writing, and Critical Revision. SS and LMK: Data Collection, Data Analysis, Draft Writing, and Critical Revision. MS, HH, FB: Conceptualization, Data Collection, Draft Writing, and Critical Revision.
- **Conflict of Interest**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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