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ORIGINAL ARTICLE

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Thymolipomatous myasthenia gravis outcomes following thymectomy: a systematic review

Zeead M. Alghamdi [a,*], Sharifah A. Othman[a], Mohammed Sabry Abdelmotaleb[a,b], Farouk Alreshaid [a], Abdullah Alomar[a], Mohammed Alaklbi [a], Hatem Y. Elbawab [a] and Yasser Aljehani[a]

[a] Division of Thoracic Surgery, Department of Surgery, King Fahad Hospital of the University, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
[b] Cardiothoracic surgery department, Faculty of Medicine, Menoufia University, Shibin Al Kawm, Al Minufiyah, Egypt

* Corresponding author. Division of Thoracic Surgery, Department of surgery, King Fahad Hospital of The University, 31952, AlKhobar, P.O.Box 40157, Eastern province, Saudi Arabia. Tel: +966138966666, ext: 1680; e-mail: zghamdi@iau.edu.sa (Z.M. Alghamdi).

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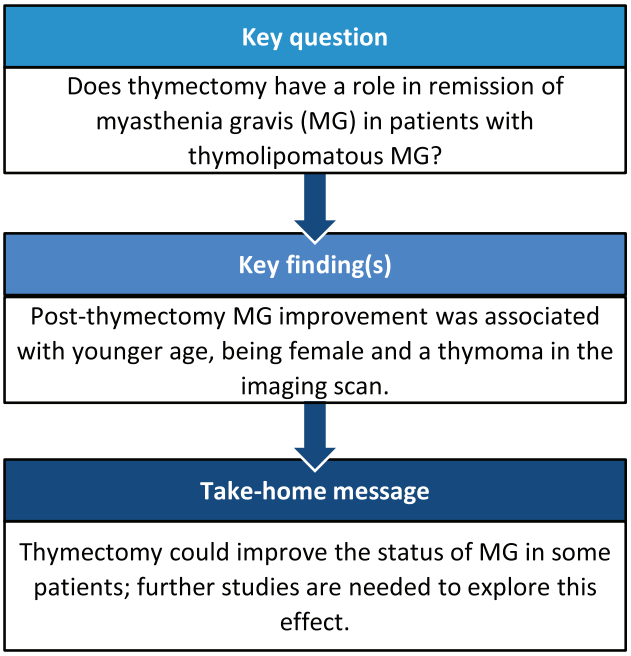

Abstract

OBJECTIVES: Our goal was to evaluate the effect of thymectomy on the progression of thymolipomatous myasthenia gravis.

METHODS: An electronic search performed across PubMed, MEDLINE and Web of Science databases included all article types. We included 15 series comprising 36 cases that met specific criteria, including case reports or case series related to thymolipoma with a myasthenia gravis association, where thymectomy was cited as the primary intervention with postoperative reporting of the prognosis and articles written in the English language.

RESULTS: Our study included 17 men (47.2%) and 19 women (52.8%). Tumour sizes varied between $34 \times 18 \times 7$ cm and $2.8 \times 2.3 \times 1.9$ cm; the weight of the tumours ranged between 38 and 1780 g (mean 190, standard deviation 341). The surgical approaches were a median sternotomy in 29 patients (80.6%), a thoracotomy in 1 patient (2.8%), video-assisted thoracoscopic surgery in 2 patients (5.6%) and unreported approaches in 4 (11.1%) patients. The disease was entirely resolved with complete, stable remission in 5 patients

(13.9%); symptoms were improved in 19 (52.8%) and stable in 10 patients (27.7%). We identified 2 groups of patients according to their improvement post-thymectomy (improved group and group with no change).

CONCLUSIONS: Although the cases were uncontrolled and did not demonstrate strong associations, they do support some hypotheses. We found a significant statistical difference between the 2 groups in terms of age, because younger patients tended to improve to a greater degree post-thymectomy. Also, we found that female patients with thymoma visible on the imaging scans were significantly associated with post-thymectomy myasthenia gravis improvement.

Registration number in PROSPERO: CRD42020173229.

Keywords: Myasthenia gravis • Outcomes • Thymectomy • Thymolipoma • Mediastinal lesions

ABBREVIATIONS

AchR-Ab	Acetylcholine receptors antibody
MG	Myasthenia gravis

INTRODUCTION

Thymolipoma is a rare, benign thymic lesion representing ∼9% of all thymic lesions and accounting for 2–9% of all thymic tumours [1]. Histologically, thymolipomas combine normal thymic tissue with mature adipose tissue. Most are asymptomatic and diagnosed incidentally. Although half of the documented cases of thymolipoma are associated with various autoimmune disorders such as myasthenia gravis (MG), Grave's disease, hypogammaglobulinaemia and lichen disease, few studies link these conditions significantly. The majority of patients are asymptomatic at the time of diagnosis. However, cough, dyspnoea, chest pain, hoarseness and cyanosis may occur due to more extensive tumours.

Although numerous theories exist concerning the pathogenesis of thymolipoma, a precise explanation is unclear, and thus, the discussion remains controversial. The foremost theory is that thymolipoma represents a neoplasm of thymic fat, with involuting thymic remnants. Another theory is based on hyperplasia, proposing diffuse thymic enlargement replaced by fatty tissue [2]. Yet others assert that the presence of thymic myoid cells stimulates the autoimmune response seen in MG and consequently plays a role in thymolipoma development [3]. Lastly, chronic use of steroids is thought to play a significant role in the fatty degeneration of thymoma and therefore stimulates the transformation from thymoma to thymolipoma, particularly in MG patients who have received steroids prolonged period [1, 4].

The incidence of thymolipoma in MG patients appears to be greater in an older population; with a mean age of 53 years, and no gender bias [5]. Some documented cases reported improved MG symptoms following complete resection of the thymolipoma [3]. We conducted a systematic review of all reported cases to summarize and analyse existing evidence. The goal was to evaluate the effect of thymectomy on the progression of MG patients with thymolipomas.

To the best of the authors' knowledge, we are reporting the largest and most comprehensive systematic review of published cases on the association between thymolipoma and MG.

Although this systematic review of case series and reports may not fully support an underlying pathological association between thymolipomas and MG disease, we hope to generate some hypotheses for future studies.

METHODOLOGY

Data sources and searches

An electronic search performed across PubMed, MEDLINE and Web of Science Databases included all article types. Keywords used were: thymolipoma, thymolipoma and MG, thymolipoma in MG and thymolipomatous MG. There were no identified retrospective nor prospective cohort studies, and the available articles utilized both case series and reports.

Study selection

No date limits for publication were applied to the literature search. All results were reviewed, and we included articles that met the following criteria:

1. Any case report or case series study related to thymolipoma with an MG association.
2. Thymectomy is cited as the primary intervention in the case, with postoperative reporting of the prognosis.
3. English-language articles.

Exclusion criteria included:

1. Any case of thymolipoma not associated with MG.
2. MG associated with other types of thymus lesions.
3. Any case without a histopathological description.
4. Any case not treated surgically by thymectomy.
5. Articles are written in a non-English language.

Of 105 items identified, a total of 15 series comprising 36 cases met the inclusion criteria for review and analysis (Fig. 1).

Data extraction and quality assessment

One author extracted data from the database, with the re-evaluation performed by a second author. The data from the studies were analysed concerning the following: the patient's age at the time of thymolipoma diagnosis and time of surgery, the patient's age at the time of MG diagnosis, gender, length of hospital stay, body mass index, co-morbidities, acetylcholine receptors antibody (AchR-Ab), MG-related symptoms, thymic lesion-related symptoms, MG medications, radiological features, surgical approach, histopathological findings, tumour size,

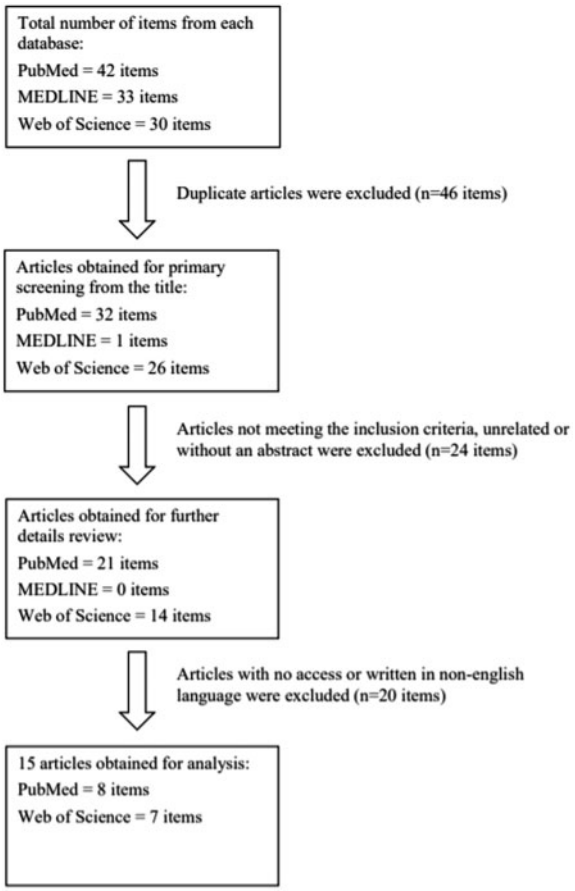

Figure 1: Study selection flowchart.

tumour weight, complications, follow-up and progression of MG post-thymectomy (Appendices 1.1 and 1.2).

A modified tool version as described by Haneline [6] for the quality appraisal of case reports was used in this study. The primary assessment was conducted by one of the authors and re-appraised by another one. Our study addressed the risk of bias by applying the following 4 criteria and rating each case according to the items with a response of yes, partially or no.

1. MG was described in all patients before being diagnosed with thymolipoma.
2. An accurate diagnosis of MG and thymolipoma was documented.
3. MG disease duration was cited clearly in the case.
4. All patients underwent a thymectomy as the treatment of choice.

Data synthesis and analysis

The Statistical Package for the Social Sciences (IBM Corp. Released 2015. IBM SPSS Statistics for Macintosh, Version 23.0, Armonk, NY, USA: IBM Corp.) was used. Data were summarized using descriptive statistics, with means and standard deviations for continuous variables. The categorical variables are described in frequencies and percentages. The patients were then divided into 2 groups according to their postoperative MG progression. Comparison between the 2 groups was made by using independent samples *t*-test, with the level of the significant set at $P \leq 0.05$.

This study registered in PROSPERO (ID: CRD42020173229).

RESULTS

Publication characteristics

A total of 105 reports from 3 databases were identified (Fig. 1). We excluded 46 reports due to duplication. Cases not meeting our inclusion criteria, unrelated to our subject or not providing an available abstract were excluded ($n = 24$ items). We excluded 20 articles as we were unable to achieve access to the article. We retained a total of 15 articles for analysis. The bibliographic references for the reported cases are included in Appendices 1.1 and 1.2.

Quality appraisal

Cases included in our study demonstrated good to moderate quality based on the items used to address the risk of bias in the above quality assessment section. All (100%) of the involved MG cases were found to have a thymolipoma post-thymectomy. The duration of MG was documented in 27 cases out of 36 (75%). In addition, most (75%) displayed evidence of MG diagnosed by the presence of AChR-Ab. All patients (100%) underwent a thymectomy as a treatment option.

Patient characteristics

The details of all involved cases, including the author's name, patient's gender, patient's age upon thymolipoma and MG diagnosis, patient's clinical symptoms, prescribed medications and the status of AChR-Ab, are listed in Appendix 1.1.

The mean patients' age at the time of thymolipoma diagnosis was 47.4 ± 14.7 years (from 16 to 76 years), and their mean age at diagnoses with MG ranged was 46.4 ± 14.8 years (from 18 to 76 years). The ratio of male to female patients was 1:1.1, with 17 males (47.2%) and 19 females (52.8%). Regarding AChR-Ab status, 21 patients (58.3%) had a positive result, while 5 (13.9%) had a negative result. In 9 cases, the AChR-Ab status was not mentioned. As clearly demonstrated in Appendix 1.1, most patients were suffering from MG symptoms such as ptosis, diplopia, dysphonia, dysphagia and limb weakness. They were receiving pyridostigmine, steroids and plasmapheresis as ongoing treatments.

Surgical and pathological features

Surgical and pathological features, including symptoms, radiological findings, surgical approach, pathology report, tumour size, tumour weight, complications, follow-up schedule and recurrences, were summarized in Appendix 1.2 and Table 1. Tumour size varied between $34 \times 18 \times 7$ cm to $2.8 \times 2.3 \times 1.9$ cm, while the mean weight of tumours 190 ± 341 g (from 38 to 1780 g). Nine cases had no documented tumour weight.

We analysed the radiological presence of a mediastinal mass in each case. Based on the results, we found 18 patients (50%) with normal chest computerized tomography scan and 18 patients (50%) with thymoma (Table 1). All patients in the study underwent a thymectomy. The surgical approaches vary from median sternotomy in 29 patients (80.6%), a thoracotomy in 1 patient

Table 1: Demographics, laboratory data, radiological data, surgical approach and prognosis of MG in 36 patients

Variables		Value
Patient characteristics		
Age (years)	Mean ± SD (range)	47.4 ± 14.7 (16–76)
Gender	Male/female (%)	17/19 (47.2/52.8%)
MG Data		
Age of patient at diagnosis of MG	Mean ± SD (range)	46.4 ± 14.8 (18–76)
AChR-Ab results	Positive/negative (%)	21/5 (58.3/13.9%)
Duration of MG (years)	Mean ± SD (range)	4.7 ± 5.1 (1–20)
Radiological findings	Thymoma (%)	18 (50%)
	No mediastinal mass (%)	18 (50%)
Surgical approach	Sternotomy thymectomy (%)	29 (80.6%)
	Thoracotomy thymectomy (%)	1 (2.8%)
	VATS extended thymectomy (%)	2 (5.6%)
	Unknown approach (%)	4 (11.1%)
Weight of the tumour (g)	Mean ± SD (range)	190 ± 341 (38–1780)
Progression of MG post-thymectomy	Complete stable remission (%)	5 (13.9%)
	Improved symptoms (%)	19 (52.8%)
	Stable MG or no improvement (%)	10 (27.8%)
	Late recurrence of Symptoms (%)	1 (2.8%)
	No data	1 (2.7%)

AChR-Ab: acetylcholine receptors antibody; g: grams; MG: myasthenia gravis; SD: standard deviation; VATS: video-assisted thoracoscopic surgery.

(2.8%), to video-assisted thoracoscopic surgery in 2 patients (5.6%). The surgical approach was unreported in 4 (11.1%) cases. The quality of thymectomy was reported in 16 patients as extended thymectomy while the remaining 20 patients, there was no documentation concerning the extension of thymectomy (Appendix 1.2 and Table 1).

Outcomes

We tracked and analysed the postoperative progression of MG in each patient (Appendix 1.2 and Table 1). The disease was entirely resolved with a complete stable remission in 5 patients (13.9%); symptoms were improved in 19 (52.8%) and stable in 10 patients (27.7%). One patient (2.8%) had a late recurrence (case #18) 2 years post-thymectomy, with no details of the surgical approach in this case. In addition, one case (#19) contained no details of either a follow-up history or progression report of the disease post-thymectomy.

Postoperative complications were reported in 2 patients (cases #19 and #21), with suppurative mediastinitis and a postoperative exacerbation of MG, respectively.

In studying the effects of thymectomy on MG with thymolipoma pathology, we identified 2 groups of patients. First, a group with improvement markers, including a complete stable remission or a lessening of symptoms. The second group contained patients with relatively no change in their symptoms or those with a late recurrence. We found a significant statistical difference between the 2 groups in terms of age, as younger patients tended to improve to a greater degree post-thymectomy than older patients. Also, we found that female patients with thymoma in the imaging scanning were significantly associated with post-thymectomy MG improvement. There was no apparent statistical difference in the AChR-Ab status, duration of MG, the surgical approach and the tumour's weight in relation to the thymectomy outcome in this group of patients (Table 2).

DISCUSSION

Thymolipoma is an uncommon, slow-growing, benign form of thymic lesion. Reported initially by Hall in 1949, it accounts for ∼9% of all thymic tumours, with a worldwide incidence of 0.12 in 100 000 cases per year. The exact underlying pathogenesis of thymolipoma remains unknown. However, steroids are thought to play an essential role in the fatty degeneration in thymoma, which may then stimulate a transformation from thymoma to thymolipoma [5]. Most of the authors surveyed in our study preferred a theory suggesting that fatty regression of a hyperplastic thymus is the underlying cause of thymolipoma. Moreover, according to a study by Rieker *et al.*, it may be difficult to differentiate these hyperplastic tumours from hyperplasia of other varieties [4]. In that particular case series, a small capsule with a strand-like deposit of healthy thymic tissue within a large amount of thymic fat tissue was observed. Further genetic studies are recommended to explore the diversity between types of hyperplasia and their relationship to thymolipomas [4].

The incidence of association between MG and thymolipomas accounts for 2.8% in one study. However, the pathogenesis behind the relationship is still unclear [7]. Some studies linked the association to the presence of thymic myoid cells triggering the autoimmune response in MG patients, as its antigen is higher in patients with MG than thymoma patients without MG [8].

This type of anterior mediastinal tumour typically occurs in patients of an older age [5]. Pan *et al.* concluded that non-MG patients with thymolipoma are often younger than patients with a thymolipoma who also present with MG [7, 9]. Our comprehensive literature review revealed that most MG patients with a thymolipoma were more than 50 years old, with a tumour weight of <100 g.

In general, thymolipomas can weigh from 10 g to as much as 6000 g [1]. The tumour weight in our reviewed cases ranged between 38 and 1780 g. The presence of compression symptoms, including cough, dyspnoea, chest pain, hoarseness and cyanosis, may occur in a large thymolipoma tumour. In our review of 36 cases, the size and the weight of the tumour were documented

Table 2: The outcomes comparison for the effect of thymectomy in the regression of MG disease between 2 groups (Group 1: improved/Group 2: no change)

Variables		Improved ($n = 24$)	No change ($n = 11$)	*P*-value
Age (years)	Mean ± SD (range)	42.2 ± 14.1 (16–67)	56.6 ± 9.2 (45–76)	0.004
Gender	Male	9	8	0.054
	Female	16	3	
Age of patient at diagnosis of MG	Mean ± SD (range)	40.9 ± 12.8 (18–59)	54.1 ± 13.7 (35–76)	0.022
Ach-Ab receptor result	Positive	12	8	0.093
Duration of MG (years)	Mean ± SD (range)	4.7 ± 4.5 (1–20)	5.1 ± 6.6 (1–18)	0.87
Radiological findings	Thymoma	9	8	0.054
	No mediastinal mass	16	3	
Surgical approach	Sternotomy thymectomy	20	9	0.64
	Thoracotomy thymectomy	0	1	
	VATS thymectomy	2	0	
	Unknown approach	3	1	
Weight of the tumour (g)	Mean ± SD (range)	214 ± 421 (38–1780)	160 ± 193 (40–680)	0.70

g: grams; MG: myasthenia gravis; SD: standard deviation; VATS: video-assisted thoracoscopic surgery.

in 13 patients. Interestingly, the patient with a tumour weight of 1780 g was asymptomatic in one study (Appendix 1.2) [10].

Chest computerized tomography and magnetic resonance imaging are the most utilized diagnostic methods, which in thymolipoma cases may reveal a lesion comprised of soft tissue and fat [11]. In total, 18 patients (50%) had no suspicion of mediastinal mass in their radiological study. There was a significant association between patients with no mediastinal mass on radiological imaging and patients with improved MG symptoms following thymectomy. Thymolipoma was diagnosed incidentally in 30–50% of patients with this association, and the diagnostic confirmation is made histologically [3, 12].

The treatment of thymic lesions involves a combination of complete resection, external beam radiation, and cisplatin or ifosfamide chemotherapy. Histological findings and disease staging are used in determining the optimum course of therapy. In the case of thymoma, surgical removal is perceived as the principal course of treatment whenever appropriate [4]. Surgical approaches may include sternotomy, transcervical, thoracotomy, subxiphoid, video-assisted thoracoscopic surgery or robotic thymectomy. In our review, 29 patients (80.6%) received a sternotomy thymectomy; 1 (2.8%) received a thoracotomy thymectomy and 2 patients (5.6%) underwent right-sided video-assisted thoracoscopic extended thymectomies. In 4 patients (11.1%), a thymectomy was performed without referring to the surgical approach. There was no specific relationship between the choice of surgical approach and the tumour size or the patient presentation. In a study by Masaoka *et al.* [13], it was articulated that an extended thymectomy including adipose tissue resection is an optimum operative approach for MG. Furthermore, Monden *et al.* [14] compared the results of patients undergoing a simple thymectomy versus an extended thymectomy in patients with thymomatous MG. He demonstrated that the prognosis of extended thymectomy in patients with thymomatous-associated MG was more favourable than for those undergoing a simple trans-sternal thymectomy. In our study, only 16 (44.4%) cases documented the extent of surgery as an extended thymectomy, 13 (36.1%) showed improvement in MG status postoperatively, and 1 case had a late recurrence of MG symptoms.

It has been reported in many studies that thymectomies are particularly beneficial in MG patients presenting with thymic tumours. It is further advocated that younger patients and those with preoperative symptoms of a short duration benefit the most from a thymectomy [15]. Our review found that patients of a young age tend to improve significantly more following a thymectomy than older patients. In addition, female patients showed a significant association with improvement post-thymectomy as opposed to males.

One case reported a recurrence 2 years following surgical excision but with no details regarding the surgical approach. Unfortunately, with only a few cases recording the postoperative period, follow-up data are not easily analysed. During this time frame, though, some of the cases did report an improvement in the symptoms of MG following a thymectomy and complete resection of the thymolipoma [1]. Unfortunately, in terms of a comparison between patients with thymomatous and non-thymomatous MG, there is limited information regarding thymolipoma surgical outcomes [5].

In this study, the progression of MG after thymectomy was assessed according to each patient's presentation. Of all patients reviewed, 19 (52.8%) had a gradual reduction in MG symptoms, 5 (13.9%) experienced complete stable remission. One patient (2.8%) reported a recurrence of symptoms; one had a recurrence within 3 weeks. Ten patients (27.8%) either stabilized their MG symptoms or saw no improvement. In general, 66.7% of patients experienced an improvement in their MG status postoperatively. Our study demonstrated this as a significant age-related association between the group who improved and the group with no apparent improvement.

CONCLUSION

Our systematic review comprises a comprehensive literature search with specific inclusion and exclusion criteria. It is important to note that the case series and reports we included are uncontrolled. Although they did not demonstrate strong associations, they do support some hypotheses. Due to a paucity of reported cases worldwide, the review provides some clues. Still, it is not robust enough to base statistical reasoning on or form conclusions. Hence, further studies are recommended in exploring the effect of thymectomy on the status of thymolipoma-associated MG.

Conflict of interest: none declared.

Data Availability Statement

All data are incorporated into the article.

Authors contributions

Zeead M. Alghamdi: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing. **Sharifah A. Othman:** Data curation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing. **Mohammed Sabry Abdelmotaleb:** Data curation; Methodology; Writing – original draft; Writing – review & editing. **Farouk Alreshaid:** Data curation; Methodology; Writing – original draft; Writing – review & editing. **Abdullah Alomar:** Data curation; Methodology; Writing – original draft; Writing – review & editing. **Mohammed Alaklbi:** Data curation; Methodology; Writing – original draft; Writing – review & editing. **Hatem Y. Elbawab:** Data curation; Methodology; Writing – original draft; Writing – review & editing. **Yasser Aljehani:** Data curation; Methodology; Writing – original draft; Writing – review & editing.

Reviewer information

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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