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CASE REPORTS

Thymus Hyperplasia and Thymoma Type B in Patients with Myasthenia Gravis: Two Case Reports and Literature Review

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Abstract

Introduction: The thymus gland plays a pivotal role in immune system regulation. However, conditions such as thymic hyperplasia (TH) and thymoma pose distinct clinical challenges due to their rarity and complex presentation in surgical practice. Both conditions can mimic similar symptoms, particularly in patients with Myasthenia Gravis (MG), where surgery serves as both a diagnostic and therapeutic intervention. This report presents the surgical management and outcomes of two MG patients with distinct thymic pathologies, TH, and Type B thymoma, alongside a review of the relevant literature.

Two MG patients were referred to our clinic for surgical intervention. The first patient underwent a standard sternotomy for the resection of TH, while the second patient underwent a mini-sternotomy for thymectomy targeting a Type B thymoma. Both procedures were completed successfully with uneventful postoperative courses. Surgical resection remains the gold standard for the treatment and definitive diagnosis of thymic gland abnormalities. Advances in surgical techniques, including minimally invasive approaches, offer excellent outcomes with reduced morbidity, providing a viable alternative to traditional methods.

Conclusion: The cases underscore the critical role of surgical intervention in managing thymic pathologies in MG patients. Traditional and minimally invasive techniques yield excellent clinical outcomes, reinforcing their importance in the thymic hyperplasia and thymoma treatment paradigm. Further studies are needed to refine surgical approaches and optimize patient outcomes.

Keywords: Thymoma, Thymic Hyperplasia, Myasthenia Gravis, Surgical Resection, Minimally Invasive Surgery

Introduction

The thymus is located in the anterior of the chest cavity and is essential for developing T-lymphocytes. After puberty, the thymus naturally shrinks in size, but certain pathological conditions can lead to thymic enlargement or tumor formation. Among these conditions, hypertrophic thymus (HT) and thymoma are distinct entities with varying causes, clinical presentations, and treatment approaches [1]. The hypertrophic thymus is typically a benign condition characterized by an enlargement of the thymus gland without any signs of cancerous changes. It is often associated with stress, infections, or autoimmune diseases. Myasthenia Graves' disease in 50-70% of cases have thymic hyperplasia [2]. This condition may have no symptoms or may present with non-specific signs such as chest pain or cough, often leading to incidental findings on imaging tests [3].

Meanwhile, a thymoma is a tumor originating from the thymus gland's epithelial cells. It is the most common tumor in the anterior part of the chest cavity in adults and can range from benign to highly aggressive. Based on cancer registry data, the overall incidence of thymoma is estimated to be 0.13 per 100,000 person-years. Thymomas are often associated with paraneoplastic syndromes, particularly myasthenia gravis, which occur in 30-50% of patients with thymoma and can cause symptoms that suggest local invasion [4].

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The surgical management of HT and thymoma is vital in treatment and/or appropriate diagnosis to manage these clinical conditions. This article reports two cases, HT and thymoma, surgical treatment, emphasizing the importance of accurate diagnosis, staging, and personalized treatment plans.

Case 1

A 20-year-old female patient is admitted to the Neurology Department, University Hospital Center "Mother Theresa," with complaints of difficulty swallowing, difficulty speaking, and ptosis of the eyelids. The patient was diagnosed with Myasthenia Gravis a year ago, with worsening symptoms recently. She started treatment with Mestinon three months ago and later with prednisolone.

The neurological examination is normal except for the partial eyelid ptosis. A computed tomography scan showed thymus hypertrophy. In the conditions when she was refractory to the medication, she was scheduled to be transferred to the cardiac surgery service for intervention. All laboratory examinations were standard. Acetylcholine receptor antibodies were positive, with a value of 106 nmol/l from a standard range of 0.1 nmol/l. The intervention was performed through median sternotomy under general anesthesia, taking special care of the specifics of the pathology. The thymus is exposed and then resected up to the border of the phrenic nerve bilaterally. The resected lobes are sent for histopathological examination. The patient was dismissed on the fifth day after surgery, with no complications, to continue the therapy with Mestinon, Azathioprine, and Prednisone. She was referred back to the neurology department. Post-operative showed an exceptional clinical amelioration within one month after intervention.

The following is a picture of the CT scan of the patient where thymus hyperplasia is evident.

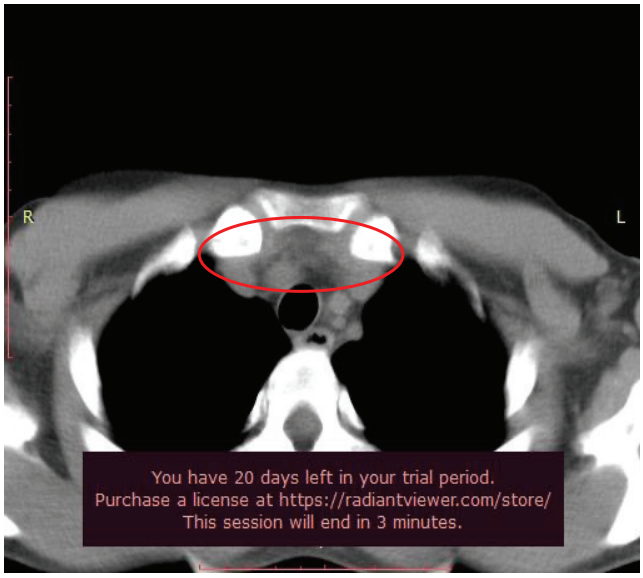

Figure 1. CT scan image of thymus hyperplasia

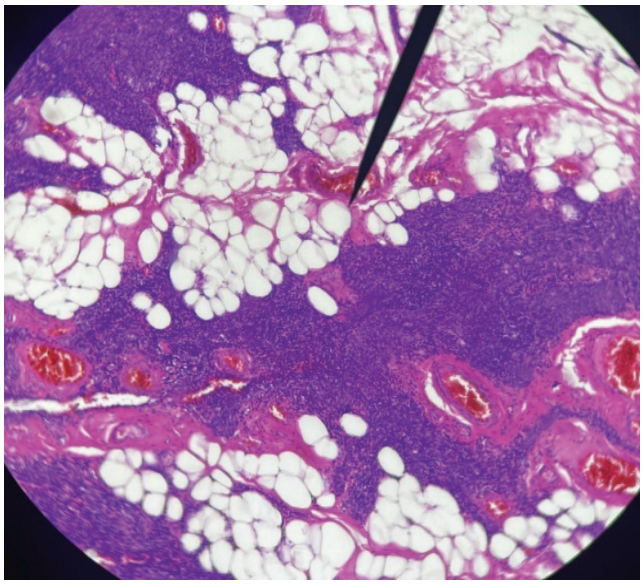

Figure 2. Thymus Hyperplasia

The histopathological analysis reveals normal components of the thymic gland, normal cortex, medulla, and Hassall corpuscles with maintained lobular configuration and preserved corticomedullary junction (Figure 2).

Case 2

A 62-year-old male patient presents to the Neurology Service with complaints of difficulty in swallowing, nasal voice, and tongue numbness. He reports that these complaints started a month ago. All the laboratory examinations were normal except for Acetylcholine receptor antibodies, which were positive 8.5 U/ml from less than 0.4, defined as a negative value. He was diagnosed with Myasthenia Gravis and started on treatment with Mestinon® and Prednisolone. A mediastinal mass, 4 X 4 cm, is noted on a CT scan in the thymus area with an indication for surgery. For this reason, the patient is transferred to the cardiac surgery service.

The surgery is performed under general anesthesia through the right "J" upper hemi sternotomy. Upon exposure, a mass in the anterior mediastinum is observed, which is suspected to be a thymoma. The mass is macroscopically firm on palpation and gelatinous in appearance internally. It is densely adhered to the bilateral phrenic neurovascular bundle and has adhesions to the brachiocephalic vein. The mass is carefully dissected and successfully resected for histopathological analysis.

The patient was discharged on the fifth day after surgery with no further complications and was referred to the neurologist and oncologist for additional follow-up. The microscopic description of the mass shows evidence of solid cellular proliferation divided by fibrotic septa.

The histopathological picture suggests a Thymoma B3. Histopathology showed a lobulated architecture comprised of cellular lobules intersected by sharply demarcated fibrous bands (A). perivascular space, small vessels surrounded by palisading neoplastic cells and scattered thymocytes (B). (Figure 3)

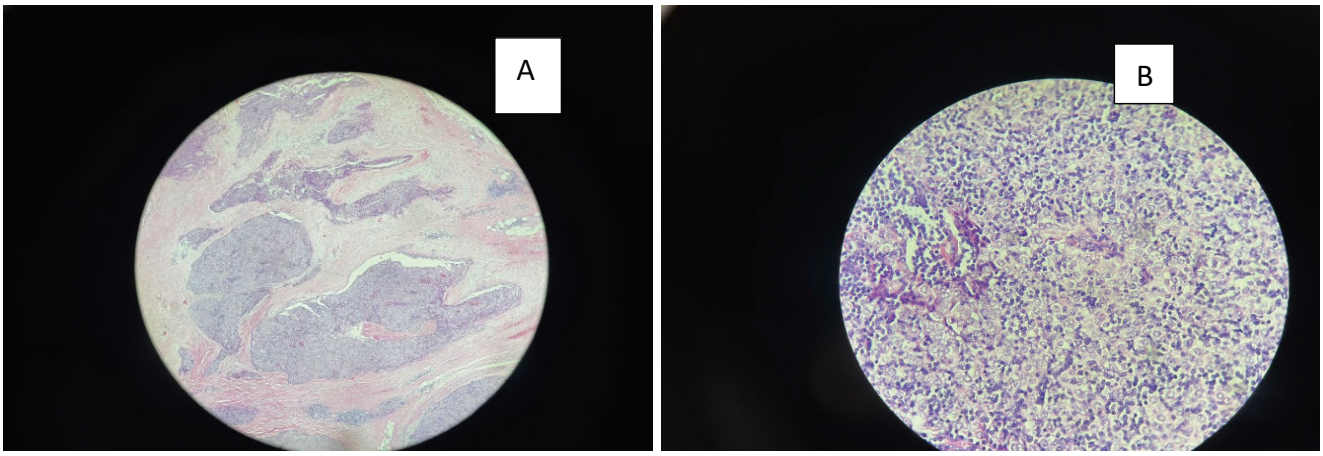

Figure 3. Thymoma Type B.

Figure 4. Thymoma operation room pictures

Discussion

Thymic hyperplasia and thymoma are different pathologies in the same organ that can appear with similar clinical signs.

Thymic hyperplasia is an enlarged thymus gland that typically retains its usual structure and can be caused by factors like chronic stress, infections, or autoimmune conditions, leading to thymic hyperplasia [5]. Sometimes, hypertrophic thymus can occur as rebound hyperplasia after chemotherapy or corticosteroid treatment, where it regains its size after shrinking [6].

Hypertrophic thymus usually has no symptoms and is accidentally discovered during imaging for other issues. When symptoms do occur, they typically involve compression of nearby structures, like the trachea or esophagus, causing breathing or swallowing difficulties [7].

Meanwhile, myasthenia Graves' disease appears in 50-70% of MG patients who have thymic hyperplasia [2]. It is a neurological autoimmune disease caused by autoimmunity against the acetylcholine receptor component of the neuromuscular junction. The lymph-follicular form of thymic hyperplasia is involved in the pathogenesis of myasthenia gravis with anti-acetylcholine receptor antibodies.

T-cell-dependent autoantibodies attack the acetylcholine receptors on the postsynaptic membrane, leading to muscular weakness. Laboratory studies may show positive Acetylcholine receptor antibodies. All the imagery examinations are helpful diagnostic tools, but chest CT scans and chest MRIs are the most used [8].

The approach to managing thymic hypertrophy is generally conservative. Surgical intervention is reserved for cases with severe symptoms or uncertain diagnosis. The indications for surgery are short as follows:

- Symptomatic Compression on adjacent mediastinal structures, causing significant symptoms such as dyspnea, chest pain, or dysphagia.
- In diagnostic uncertainty, where imaging cannot distinguish hypertrophic thymus from a neoplastic process, a biopsy or partial resection may be necessary for a definitive diagnosis.
- Association with cases where thymic hypertrophy is associated with autoimmune diseases that are poorly controlled or refractory to medical therapy [9].

Yoshimatsu et al. reported the results of thymectomy in a study including 427 patients with autoimmune disorders such as Myasthenia Gravis and ulcerative colitis nonresponsive to conservative therapy where thymectomy was performed. Follow-up observation from 2 to 17 years after surgery revealed complete recovery and significant improvement in 100 (75%) out of 133 patients with nontumorous thymic abnormalities. In total, follow-up observations showed that 84% of patients were inactive after thymectomy compared with 50% before the operation [10]

Nazarbaghi et al. report that extended transsternal thymectomy, along with a postoperative regimen of prednisolone and pyridostigmine, regardless of the preoperative duration of MG, is a safe and effective treatment modality for MG patients with either thymoma or thymic hyperplasia.[11]

Is thymectomy beneficial in non-thymomatous myasthenia gravis? A definitive study on the effectiveness of thymectomy in non-thymoma MG patients has not been done. The role of this procedure remains uncertain, but the evidence we have currently is from Class II studies, and the existing data seem to support an extended resection that removes as much thymic tissue as possible [12].

Surgical Approach used in cases of hypertrophic thymus: thymectomy is generally a minimally invasive approach, such as video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracic surgery (RATS), but also total surgical excision via open sternotomy is advised when thymic hypertrophy is not a specific diagnosis. In any case, the gold standard approach for thymectomy is a median sternotomy or transsternal approach. [13]

Our case underwent medical therapy for several months but was refractory to the treatment. The surgical method was a natural part of the treatment in these conditions. The standard sternotomy was the approach of entry. We have performed a full sternotomy to be sure of the total resection of the hyperplasic thymic tissues. The postoperative course was excellent. The patient had a distinguishable amelioration of the myasthenia signs one month after intervention.

Thymomas

Thymomas are tumors in the thymus gland made up of epithelial cells. They are classified based on their characteristics and invasiveness. The World Health Organization categorizes thymomas as Type A (benign), Type B (mixed), and Type C (thymic carcinoma), indicating increasing malignancy and poor prognosis [14]. Thymomas are linked to genetic mutations and changes in the thymic environment, though the exact cause is not fully understood [15].

Symptoms and Diagnosis

Thymomas can cause various symptoms depending on size, location, and invasiveness, including chest pain, coughing, breathing difficulties, or systemic issues like myasthenia gravis or anemia. Imaging tests such as chest X-rays, CT scans, and MRIs are crucial for diagnosing and managing both hypertrophic thymus and thymomas. PET scans can help differentiate thymomas from benign thymic hyperplasia based on metabolic activity, but a histopathological analysis is needed for a definitive diagnosis.

If imaging results are inconclusive, a biopsy may be required to confirm the diagnosis. Under imaging guidance, FNA or core needle biopsies can be performed to collect tissue samples for examination, though thymoma biopsies require caution to avoid tumor spread [3]. Sometimes, surgical removal is necessary to obtain a proper tissue sample and completely remove the tumor.

Indications for Surgery

Surgical resection is the cornerstone of thymoma treatment with the following primary objectives:

- *Complete Tumor Resection:* The goal of surgery in thymoma cases is to achieve a complete (R0) resection, where no microscopic tumor remains. Complete resection is associated with the best long-term outcomes and is particularly crucial in early-stage thymomas.
- *Symptomatic Relief:* Surgery may also be indicated to alleviate symptoms related to mass effect, such as superior vena cava syndrome, which can result from the tumor compressing the superior vena cava.
- *Reduction of Paraneoplastic Syndromes:* Thymectomy is often performed in patients with thymoma-associated myasthenia gravis, as removal of the tumor can lead to significant improvement or remission of the autoimmune symptoms [16].

One of the most recent significant reviews on this topic was by *Zhang Y.et al.* [17], which reviewed articles published from January 1995 to January 2023. The authors reported that surgery remains the primary treatment modality for palliating cancer-related symptoms and prolonging life. The surgeon's experience and skill with this type of patient are critical [17].

VATS and RATS have become standard approaches for early-stage cases. For advanced-stage thymoma, radical resection is considered the primary therapy, though since surgery alone does not necessarily control the disease, a multimodality treatment strategy is often needed [18].

Detterbeck et al., correlating outcomes with surgical approaches and adjuvant therapies, report the critical role of surgery in the management of thymoma [19].

Also, a study published by *Kanzak R.* in 2018 in the Journal of Interactive Cardiovascular and Thoracic Surgery debated the role of multimodal therapy, preoperative chemotherapy, or chemoradiotherapy followed by surgery. It concluded that preoperative chemotherapy or chemoradiotherapy followed by surgery for locally advanced thymoma can be performed with an acceptable degree of surgical risk. Such a strategy should be proactively considered, as it can lead to favorable long-term results [20]

Surgical Approach

The choice of surgical technique depends on the stage of

the thymoma, the patient's overall health, and the surgeon's expertise. The stage is based on the Masaoka-Koga staging system, which classifies thymomas based on tumor invasion and metastasis [21]. Staging is crucial for determining surgical resection, additional therapies, and prognosis [22].

- Stage I indicates complete encapsulation of the tumor without invasion.
- Stage II involves microscopic or noticeable invasion into adjacent tissues.
- Stage III shows macroscopic invasion into nearby organs.
- Stage IV includes spread to pleura or distant metastases.

Surgical approaches include median sternotomy and less invasive VATS or RATS. Sternotomy remains the most common approach for thymectomy in thymomas, particularly in extensive or invasive thymomas (Masaoka-Koga stages III and IV), where extensive dissection may be required. Video-assisted thoracic surgery (VATS) and Robotic-Assisted Thoracic Surgery (RATS) are increasingly used in the resection of early-stage thymomas (Masaoka-Koga stages I and II).

Outcomes depended on the stage of thymomas. Stage I & II: The outlook is very good with just surgical removal, which is linked to low recurrence rates. Adjuvant radiation might be suggested for Stage IIb with positive margins [1]. Stage III: Expectations can vary greatly; surgery is usually combined with additional therapies to improve results. The extent of resection and completeness of tumor removal are critical factors for long-term survival [21, 22]. Stage IV: The prognosis is typically unfavorable, especially in Stage IV-b instances. A combination of treatments involving surgery, chemotherapy, and radiation is generally needed, with an emphasis on supportive care for advanced cases [22].

In our case, we used mini-sternotomy as an entering approach. The patient had an uneventful post-operative course.

Postoperative Care and Monitoring: Postoperative care for individuals with enlarged thymus and thymoma varies significantly. Patients who undergo thymectomy for an enlarged thymus generally have a good outlook and may not need long-term follow-up, except in cases with autoimmune disorders. Follow-up imaging may be done to confirm symptom resolution [23].

Conversely, patients with thymoma require more thorough postoperative care, especially in advanced stages. Regular imaging exams are typically needed to monitor for recurrence. Those with Stage II or higher thymomas may receive additional radiation therapy. Chemotherapy or targeted therapies may be necessary for cases where the tumor hasn't been fully removed or if there are signs of spread [3].

The long-term outcome of thymoma patients is affected by the stage at diagnosis, the extent of surgery, and the effectiveness of follow-up treatments. Continuous monitoring is essential to detect recurrences early and manage potential complications from radiation [24].

Conclusions

Resection of hyperplasic thymus or thymomas remains the gold standard for treatment and/or definitive diagnosis. Standard surgical or minimally invasive approaches can be performed with excellent results.

COI Statement: This paper has yet to be submitted in parallel, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

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Abbreviations

TH - Thymic Hyperplasia; MG - Myasthenia Gravis; HT - Hypertrophic Thymus; VATS - Video-Assisted Thoracoscopic Surgery; RATS - Robotic-Assisted Thoracic Surgery;

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