Perioperative Enduring Voyage in a Myasthenia Gravis Patient who Underwent Combined Thymectomy and Thyroidectomy: A Case Report and Review of Literature

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Abstract

Combined Thymectomy and Thyroidectomy in Myasthenia Gravis patient remains a greater challenge to both surgeon and anesthesiologist due to complexity of surgery and risk associated during management of Myasthenia Gravis patient. Association of mass with major vessels, pleura and pericardium during surgical dissection followed by Myasthenic crisis and prolonged mechanical ventilation pose a greater challenge. Thoracoscopic extended Thymectomy has shown a superior short term outcome compared to transsternal technique. At our institute, a 65 year old female whos incidental finding was huge Thymic mass and who is not on any treatment for Myasthenia Gravis, underwent combined Transthoracic Thymectomy and Thyroidectomy under General anesthesia. In this article we would describe the management aspects, associated complications which we encountered during all the 3 stages of voyage. Along with case we combined the review of literature under 5 sub headings as Preoperative evaluation, Differential Diagnosis, Pathology and immunohistochemistry, anesthetic and surgical management and the prognosis.

Keywords: Thymectomy • Myasthenia Gravis • Thyroidectomy • Management

Introduction

Myasthenia Gravis (MG) is an autoimmune disorder characterized by fatigable weakness of skeletal muscles. Myasthenia Gravis is characterized by the development of autoantibodies against the Acetylcholine (Ach) nicotinic postsynaptic receptors at the neuromuscular junction [1]. MG is usually associated with other autoimmune disorders such as Rheumatoid arthritis, Systemic lupus erythematosus and thyroid disorders. More than 75% of patients with myasthenia Gravis have been associated with thymic abnormalities (thymic hyperplasia or thymoma) [2, 3]. Thymectomy itself is a challenging procedure because of its close relation to heart, lungs and great vessels. The challenge increases exponentially if operated on MG patients not on any treatment, because of the possibility of compromised airway and Myasthenia Crisis. Here we report a unique case of MG patient who underwent combined thyroidectomy and thymectomy at our comprehensive oncology institute along with review of literature.

Case report

A 65 year old female (BMI of 22.5) hypertensive and hypothyroid since 5 years and on regular medications comes to our oncology clinic with a huge thyroid swelling since 6 months. Chest x-ray reveals a mediastinal widening. In order to confirm the chest x-ray findings, we got CT neck and thorax; incidentally along with the thyroid swelling we noticed a large lobulated soft tissue density lesion measuring 12*10.8*7.5 cm. The mass effect was seen over left upper lobe bronchus with collapse of some portion of lung and medially extending into prevascular, pretracheal and superior mediastinum. FNAC of thyroid revealed to be a papillary thyroid malignancy (Bethesda diagnostic category- v). FNAC of mediastinal mass revealed highly cellular smear showing dual cell population comprising of tightly cohesive clusters of epithelial cell, plenty of basal nuclei and lymphocytes suggestive of thymoma. For further confirmation and characterization Immunohistochemistry (IHC) and biopsy were advised. IHC revealed scant islands of epithelial tumor with hyalinized stroma , scant focal round oval cells with moderate cytoplasm and squamoid morphology suggesting a possibility of Thymoma or thymic carcinoma(WHO classification type: Metaplastic Thymoma) as shown in Figure 1 . IHC markers which were positive are PCK (AE1/ AE3) and CK 7 (EP 16) suggestive of Thymic carcinoma.

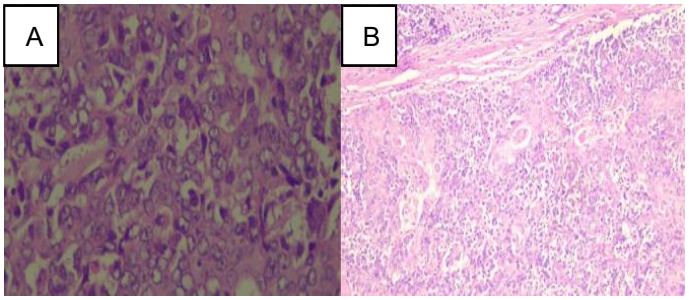

Figure 1: Scant islands of epithelial tumor with (A) Moderate cytoplasm and (B) squamoid morphology suggestive of Thymoma or Thymic carcinoma.

Routine blood investigations revealed a normal thyroid profile (T3 - 1.49 ng/ml, T4 - 7.35 microgram/ dl, TSH - 0.934 microIU/ml). To rule out and evaluate MG, on clinical examination patient only complains of unusual neck and limb muscle weakness which relieved on rest without showing any ocular signs or symptoms (class- IIIA). MG was confirmed by the most sensitive Acetylcholine Receptor (ACHr) binding antibody test (EIA) which revealed a high positive titre of 3.20 nmol/l (normal: < 0.40, borderline: 0.40-0.50, positive level>0.50). Pulmonary function test revealed a mild restrictive pattern with a vital capacity of 2.6 liter. A decremental response of 10% - 15% noticed on Repetitive Nerve Stimulation (RNS) test suggesting MG.

On discussion with a neurologist and explaining the patient, the possible outcomes, need of immunoglobulins and plasmapheresis we henceforth proceeded with the surgery. Preoperatively, the patient was started with intravenous prednisolone 60mg twice a day 3 days prior to surgery. The plan of surgery was Thoracoscopic assisted thymectomy with Thyroidectomy. Preoperatively premedication was skipped; regular steroid dose was administered on the morning of surgery. Two large bore peripheral IV cannulas were secured. All ASA standard monitors were connected to the patient. Additionally we required Radial artery cannulation for continuous intra-arterial Blood pressure monitoring, BIS monitor and a peripheral nerve monitor. General anesthesia induced with 2mg/kg propofol IV, 2mcg/kg fentanyl IV and titrating doses of atracurium (10%-25% of ED 95) with the help of neuromuscular monitoring. Tracheal intubation secured

and good respiratory effort with full consciousness, the patient was extubated without any administration of reversal agents and then shifted to ICU for further monitoring.

Postoperatively.On day 2 clinically patient was tachypneic, tachycardic and required increased oxygen support, on auscultation there is decreased air entry of the left side of chest. So, we got a chest x-ray and HRCT which revealed atelectasis and consolidation changes. Patient was supported with Non Invasive Ventilation (NIV) and antibiotics were escalated to levofloxacin. Respiratory distress decreased the following day but on POD5 patient had one episode of seizure activity which was relieved by administering 1g levetiracetam IV. Following which patient was asymptomatic and shifted to ward and discharged from hospital on POD 8.

Discussion

Preoperative evaluation

More than half of mediastinal masses are located in the anterior mediastinum [4-7]. and remaining one fourth in middle and posterior mediastinum. In adults most common mediastinal neoplasms are thymomas exhibiting variability in histological, biological and genetical [8]. Thymomas or Thymic carcinomas usually present either as an incidental finding or local compressive effects (cough, dyspnea, dysphagia, signs of superior vena cava syndrome, Horner's syndrome) or in association with other paraneoplastic syndrome.Thymic carcinomas usually present more aggressively with signs of superior vena cava syndrome, chest pain and dyspnea. 30% - 40 % of Thymic tumors have strong association with Myasthenia gravis and other paraneoplastic syndrome (cushing's syndrome, syndrome of inappropriate antidiuretic syndrome, systemic lupus erythematosus, polymyositis, red cell aplasia) [9,10]. So ruling out paraneoplastic syndrome, especially Myasthenia Gravis, is important. Myasthenia Gravis is an autoimmune disease characterized by weakness and fatigability of skeletal muscles with improvement following rest. Auto antibodies develop against postsynaptic Acetylcholine (Ach) nicotinic receptors. Levinthal scoring system has been widely accepted in predicting postoperative mechanical ventilation in MG patients who require surgery. Preoperative bulbar symptoms, history of myasthenic crisis, intraoperative blood loss >1000 ml, duration of myasthenia gravis>6 years, vital capacity <2.9 liters, history of chronic pulmonary disease, serum anti choline receptor antibody test >100 nmol/ml are the risk factors 9 included in levinthal scoring system.

In our case the patient did not show any active symptoms even in the presence of huge mediastinal mass with one positive levinthal scoring risk factor. Patient only gives a history of experiencing unusual weakness of neck muscles, limb muscle weakness with absent ocular symptoms which gets relieved on rest [as the class IIIA in accordance to the Myasthenia Gravis Foundation of America (MGFA) [10]. Tensilon test, ice pack test, electromyography test and anti- AChr antibody test are the usual tests carried out for diagnosing MG, amongst them Anti - Achr antibody test being most sensitive. Our patient showed significant high titre of Anti - Achr antibody titre along with 15% decremental response on electromyography test. Other paraneoplastic syndromes have been ruled out like red cell aplasia, hypogammaglobulinemia (regular infections, diarrhea) and which usually present with spindle cell pathology.

Differential diagnosis

The mediastinum is the thoracic space between the pleura of the lungs comprising major vessels, nerves, trachea, and esophagus and thymus gland. Development of differential diagnosis avoids unnecessary biopsies or

Table 1. ITMIG clinical and radiological approach for mediastinal mass

Clinical Scenario	Level of Confidence	Proportion of All (%)	Type of Information
Age >40, men and women			**Demographic**
1. Consider substernal goiter - should be obvious on CT (Resect if symptomatic; rarely consider thyroid malignancy)	certain	10 - 30 %	Imaging
2. If not substernal Goiter -Thymoma most likely			
a) If MG,other than paraneoplastic syndrome	Certain	50 %	Clinical
b) If lobulated, homogenous/ slightly heterogeneous mass	High		Imaging
c) If lobulated and with pleural nodules(i.e M1a)	Very high		Imaging
Resect if early stage, core(or surgical) biopsy first if higher stage			
3. If it does not fit for Goiter/ Thymoma			
a) If well circumscribed, round/ oval/ saccular and homogeneous near thymic mass on CT - consider Thymic cyst & evaluate with MRI		10 – 40 %	
If pleuritic cystic- unilocular Thymic cyst, observe for 2 years	Very high	< 5%	Imaging
If cystic but with soft tissue components on CT/MRI - multilocular cyst/cysticThymoma-	Uncertain	<5 %	Imaging
Resection			Clinical
b) If heterogeneous with fat(bone) - Benign Teratoma - Resect if symptomatic/ significant organ compression	High	<5 %	Imaging
c) If matted, multiple enlarged nodes- HD, MLC -NHL	moderate	2 - 10 %	Imaging
If 'B' symptoms ↑ LDH - HD, MLC - NHL	High		Clinical
d) Everything else- various rare tumors → core(surgical) biopsy	unclear	5 - 20 %	Histology
Age 10 - 39 years, women			

1. If matted, multiple enlarged nodes, 'B' symptoms, ↑LDH→HD, MLC- NHL - core(surgical) biopsy	High	30 - 50 %	Imaging Clinical
2. If heterogeneous with fat(bone)→benign teratoma - Resect if symptomatic (or) significant organ compression	High	10- 25 %	Imaging
3. If MG & lobulated , homogeneous mass → Thymoma - Resect if early stage, core(surgical) biopsy if high stage	High	5 - 10 %	Clinical Imaging
4. If fulminant onset: a. Large mass ,pleural effusion, ' B' symptoms, ↑LDH→LB- NHL - Cytology of pleural effusion, bone marrow	Moderate	5 - 10 %	Clinical Imaging
b. Heterogeneous mass,lung metastasis→NSGCT	Certain		Cytology
-Confirm with serum α-FP, β- hcg(± biopsy)	Moderate	2 - 5%	Clinical Imaging
c. If everything else →various rare tumors	Certain		Lab (± Biopsy)
-core(or surgical) biopsy	unclear	5 - 20 %	Histology
Age 10 - 39 years, men			
1. Rapid onset of symptoms , heterogeneous mass → NSGCT or LB - NHL a. NSGCT more likely if age 20 - 30 , moderate lung metastasis	Moderate	10 - 25 %	Clinical Imaging
-Confirm with α- FP, β-hcg(± biopsy)	Certain		Lab (± Biopsy)
b. LB - NHL more likely if age 10 - 20 years, ' B" symptoms, effusion	Moderate	5 - 20 %	Clinical Imaging
-Confirm with α- FP, β-hcg(± biopsy)	Certain		Lab (± Biopsy)
b. LB - NHL more likely if age 10 - 20 years, ' B" symptoms, effusion	Moderate	5 - 20 %	Clinical Imaging
-Cytology of pleural effusion, Bone marrow	Certain		Cytology
2. Intermediate onset of symptoms			
a. If matted , multiple enlarged nodes→ HD, MLC - NHL		20 - 25 %	Clinical Imaging
b. Homogeneous → seminoma		5 - 10 %	Clinical Imaging
-core(or surgical biopsy)			
3. Asymptomatic/ Indolent onset of symptoms			
a. Thymoma more likely if age > 30 years; homogeneous- certain if MG	Moderate	10 - 30 %	Clinical Imaging
-Resect if early stage, core(or surgical) biopsy if higher stage			
b. If heterogeneous with fat (bone)→ benign teratoma (especially if age 10 - 20)	High	10 - 20 %	Imaging

Table 2: Diagnostic criteria of Thymomas

	Obligatory criteria	**Optional criteria**
Type A	Occurrence of bland, spindle shaped epithelial cells (at least focally); paucity [a] or absence of immature (TdT+) T cells throughout the tumor	Polygonal epithelial cells CD20+ epithelial cells
Atypical type A variant	Criteria of type A thymoma; in addition: comedo-type tumor necrosis; increased mitotic count (>4/2mm2); nuclear crowding	Polygonal epithelial cells CD20+ epithelial cells
Type AB	Occurrence of bland, spindle shaped epithelial cells (at least focally); abundance [a]of immature (TdT+) T cells focally or throughout tumor	Polygonal epithelial cells CD20+epithelial cells
Type B1	Thymus-like architecture and cytology: abundance of immature T cells, areas of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelia cells without clustering (i.e.<3 contiguous epithelial cells)	Hassall's corpuscles; perivascular spaces

Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells	Medullary islands; Hassall's corpuscles; perivascular spaces
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T cells	Hassall's corpuscles; perivascular spaces
MNT[b]	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma	Lymphoid follicles; monoclonal B cells and/or plasma cells (rare)
Metaplastic thymoma	Biphasic tumor composed of solid areas of epithelial cells in a background of bland-looking spindle cells; absence of immature T cells	Pleomorphism of epithelial cells; actin, keratin, or EMA-positive spindle cells
Rare others [c]		

Table 3: Markers considered being useful for the routine immunohistochemical characterization of otherwise difficult to classify thymomas and thymic carcinomas.

Marker	**Cellular and subcellular targets of mediastinal tumors**
Cytokeratins	Epithelial cells of normal thymus, thymomas [a], thymic carcinomas, neuroendocrine tumors, many germ cell tumors, rare sarcomas and dendritic cell tumors; metatases to the mediastinum
Cytokeratin 19	Epithelial cells of normal thymus, thymomas [a] and thymic carcinomas
Cytokeratin 20	Negative in normal thymus and thymomas. May be positive in rare thymic adenocarcinomas, teratomas or metastases
P63	Nuclei of normal and neoplastic thymic epithelial cells, squamous epithelial cells (e.g. in teratoma, metastasis), primary mediastinal large B-cell lymphoma
P40	Nuclei of normal and neoplastic thymic epithelial cells, squamous epithelial cells (e.g. in teratoma; metastasis)
TdT	Immature T cells of normal thymus, >90% of thymomas and neoplastic T cells of T lymphoblastic lymphoma
CD5	Immature and mature T cells of thymus and >90% of thymomas
	Neoplastic T cells of many T lymphoblastic lymphomas
	Epithelial cells in70% of thymic carcinomas [b]
CD20	Normal and neoplastic B cells
	Epithelial cells in 50% of cases of type A and AB thymoma
CD117	Epithelial cells in 80% of thymic carcinomas
	Neoplastic cells in most seminomas

tumors of lung, pleura,Thymus and Heart. [12, 13]. The revision in detail described the description of clinical symptoms, macroscopic, Resectability of tumor depends on the differentiation of thymic malignancy from hyperplasia; amongst which complete resection carries the most significant prognostic value. Post resection of tumor, the histopathological assessment plays a pivotal role for treatment decisions. For thymic carcinoma chemoradiotherapy plays major component of treatment modality [14]. In advanced Thymic carcinomas, KIT mutations have been reported and henceforth targeting angiogenesis with multikinase inhibitors plays a significant role [15]. In B2, B3 subtypes, of stage II Thymomas, [16] postoperative radiotherapy may be considered. Neoadjuvant chemotherapy has been modality of treatment in Thymomas which are resectable, unresectable and recurrent disease. Immunotherapy and Vascular Epidermal Growth Factor (VEGF) tyrosine kinase inhibitors have shown promising results in thymic carcinomas that have been refractory to initial chemotherapeutic regimen.

Anesthesia and surgical plan and management

Anesthesia considerations and management: Prolonged mechanical ventilation and Myasthenia Crisis (MC) remain the problematic aspects in anesthetic management of a patient with Myasthenia Gravis undergoing laparoscopic Thymectomy with Thyroidectomy. The risk of MC is as high as 5% – 20% after Thymectomy as reported in literature. [17, 18]. Regional anesthesia is usually preferred over General anesthesia whenever possible in these cases. General anesthesia is performed when adequate neuromuscular monitoring is available all throughout the surgery.

Premedications are generally avoided in these patients due to respiratory compromise. Anesthesia technique of choice in our patient was General anesthesia with 37F Double Lumen endotracheal tube (DLT tube) with Positive Pressure Ventilation (PPV). For induction, titrated doses of IV propofol, short acting opioids like IV remifentanil, deepening the plane for intubation with inhalation agents and avoidance of Neuromuscular Blockers (NMB) have been the usual choice [19, 20]. However, many prefer using balanced anesthesia with titrating doses of neuromuscular blocking agents (10% - 25% ED95) with inhalation agents with continuous peripheral nerve monitoring. In our case we intubated the patient with titrating doses of IV fentanyl, IV propofol, and IV Atracurium as NMB agent. Maintenance anesthesia IV dexmedetomidine in MG remains controversial due to undue bradycardia in patients who are on anticholinesterases [21]. Few studies showed hemodynamically stable on dexmedetomidine infusion in patients with Myasthenia Gravis patients [22]. So, in our case we used IV dexmedetomidine infusion with loading dose of 1.2mcg/kg for 10 minutes and followed by 0.6mcg/kg in order to decrease the opioid and muscle relaxant requirement. Hemodynamically patient was stable all throughout procedure. Surgery lasted for 200 minutes. Extubation performed after 2 hours after surgery after extubation criteria met (sustained head lift for 5 minutes, a negative inspiratory force of 25 cm H2O, and vital capacity of 15ml/kg and TOF > 0.9) without any reversal agents. Surgical approach: Transcervical, Transsternal, Thoracoscopic thymectomy are the usual approaches for thymectomy in patients with MG. Thoracoscopic Thymectomy being the recent advances with several advantages of minimal postoperative morbidity, shorter hospital stay, [23] henceforth the approach in our case was Transthoracic Thymectomy.

After intubation with DLT, on selective ventilation of the lung required, first right portion of the patient is positioned in the left lateral decubitus position, and slight flexion at middle of chest. Three ports 5mm ports were placed, two ports along anterior axillary line along inframammary fold at 5th intercostal space for utility access, second at posteroinferiorly for the camera port. Dissection proceeds from the left internal mammary vein till it meets the right internal mammary vein and superior vena cava. So, the right inferior horn must be dissected and the phrenic nerve can be identified by opening the right pleural space. Dissecting innominate and ligating thymic veins, the thymus is dissected anteriorly and laterally. So, we are left only with superior horns and right lateral border dissection along with lymph nodes dissection. (The boundaries of radical Thymectomy are mainly phrenic nerve laterally, inferiorly diaphragm and superiorly by thyrothymic ligament). For left side thoracoscopic dissection similarly patient in right

lateral position, 5mm ports are inserted on left side. First phrenic nerve is identified and dissection is preceded all the way over phrenic nerve till complete resection of thymic mass is achieved. Anterior Thymic nodes (N1) and deep thymic nodes (N2) have been dissected. R0 resection which has a critical prognostic indicator has been done since, it was a huge mass, and we required a left thoracotomy incision to excise the mass. Intercostal nerve block performed after excision of mass with 20ml of 0.2% Ropivacaine.

Post-operative ICU: After extubation, patient was shifted to intensive care unit with 4 liters of O2 support. Several strategies have been employed to decrease the chances of Myasthenia crisis and need of prolonged post-operative ventilation. But still, postoperatively, on day 2 patients was tachypneic, tachycardic and required increased oxygen support, on auscultation there is decreased air entry of the left side of chest. So, we got a chest x-ray and HRCT which revealed atelectasis and consolidation changes. NIV has shown promising results in

improving gas exchange, reducing respiratory distress, atelectasis after cardiac and thoracic surgery and henceforth decreasing the need of reintubation and improving clinical outcomes [24]. So, patient was supported with Non Invasive Ventilation (NIV) and antibiotics were escalated to levofloxacin. Respiratory distress decreased the following day but on POD5 patient had one episode of seizure activity. The antibiotics which aggravate myasthenia crisis as described in the literature are macrolides, fluoroquinolones, aminoglycosides, tetracycline and chloroquine. Levofloxacin has been widely used antibiotic and few studies showed safer use of levofloxacin compared to other fluoroquinolones [25]. In our case levofloxacin did not aggravate myasthenic crisis indeed we noticed decrease in seizure threshold resulting in seizures, which was relieved by administering 1g levetiracetam IV. Following which patient was asymptomatic and shifted to ward and discharged from hospital on POD 8.

Follow up post thymectomy: The 15 year survival rate is 12.5% and 47% in invasive and non-invasive thymomas respectively [26, 27]. AJCC TNM and Masaoka staging are the two systems used for staging and prognostication. In our case, tumor has been graded as stage 2 AJCC TNM classification which has excellent prognostic value [28]. There was no death related issues in stage 1 and stage 2 Masaoka thymomas. But Stage I to stage III thymic carcinomas because of higher risk of local recurrence studies have shown significant advantage on postoperative radiotherapy of 45Gy to 50Gy over 5 weeks [29].

It is recommended to get CT every 6 months for 5years in Thymic carcinoma and for 10 years in Thymoma. Recurrence is usually seen mostly as pleural nodules and B cell non-Hodgkin's lymphoma, gastrointestinal malignancies being the most common secondary metastasis. Further, patients with thymoma and Thymic carcinoma may require medical and radiation oncology consultation. A neurologist consultation may be required for reassessment of myasthenic symptoms whether to or till when to continue medications.

Conclusion

Thymectomy results in significant improvement in Achr antibody positive MG. Detailed preoperative history, pathology and immunohistochemistry helps in evaluation and decide to proceed for surgery, chemotherapy or radiation avoiding unnecessary tests. R0 resection and avoiding aggravating factors of Myasthenia Gravis helps in better outcome and prognostification of patient. Staging pathologically, clinically, radiologically adds on years to patients who undergo thymectomy with thyroidectomy in Myasthenia Gravis patient.

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