Myasthenia gravis and thymic neoplasms: A brief review

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Abstract

Thymoma is the most common mediastinal tumor. They have varied presentation ranging from asymptomatic incidental mediastinal masses to locally extensive tumor with compressive symptoms and distant metastases. They have frequent association with various paraneoplastic syndromes (PNS). The most common PNS associated with thymoma is myasthenia gravis (MG). Patients of thymoma with MG have a favourable outcome due to early disclosure of the disease. Histologically they are classified into five subtypes and Masaoka-Koga staging system is used for staging. Surgery, chemotherapy and radiotherapy play an important role along with anti-myasthenia drugs. This review would like to highlight the association of thymoma with MG and associated clinical and therapeutic issues.

Key words: Thymoma; Myasthenia gravis; Surgery; Radiotherapy; Chemotherapy

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Core tip: This article is a comprehensive review of literature of a rare neoplasm. This article outlines the various newer details of diagnosis, staging and treatment aspects of thymoma and myasthenia gravis (MG). The importance of association between thymoma and MG is reviewed in detail.

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INTRODUCTION

Thymoma is a neoplasm of the thymus gland originating from its epithelial tissue. Thymomas are the most common neoplasm of the anterior mediastinum in adults and the most common tumor of the thymus[1]. They account for approximately fifty percent of the anterior mediastinal masses[1]. But, thymomas are rare human neoplasms accounting for less than 0.5% of all cancers. The incidence of thymoma is 0.15 per 100000 person years[2]. The peak incidence in seen in the fourth and fifth decades of life with 52 years as the mean age at presentation[3]. No sexual predilection exists. They have frequent association with various paraneoplastic syndromes (PNS)[1]. The most common PNS associated...
with thymoma is myasthenia gravis (MG). This review would like to highlight the association of thymoma with MG and associated clinical and therapeutic issues.

CLINICAL ASSOCIATION

Thymomas are associated with PNS in 50% to 70% of cases[3]. The common PNS associated are MG (30% to 50%), Cushing syndrome, hypogammaglobulinemia, pure red blood cell aplasia, rheumatoid arthritis and limbic encephalitis. Thymoma is detected early in patients with MG as compared to patients without PNS due to regular clinical evaluation for treatment of MG[4]. The most common symptom is cough. They usually have a slow growth and spreads by local extension. Metastatic spread is to the pleura, pericardium, or diaphragm, while spread to extrathoracic sites are uncommon[2].

MG is a disease affecting the neuromuscular junction and manifests as muscular weakness and fatigability due to acetyl-choline receptor (AChR) antibodies in 85% of the cases[5]. Thymoma MG is seen in approximately fifteen percent of all MG cases[6]. Basic pathogenesis is caused by humoral immune response to an epitope on the thymoma cells which is similar to the epitope on the neuromuscular junction components[7]. The neoplastic thymoma cells encircled by the T cells expresses epitopes that cross-react with AChR. All patients with thymoma MG have detectable AChR antibodies in serum. The AChR antibody attacks the neuromuscular junction, specifically aimed at the nicotinic AChR at the endplate region of the postsynaptic membrane, resulting in muscle weakness[8]. Other non-AChR autoantibodies are also seen in 95% of thymoma MG cases and in 50% patients with late-onset MG (after 50 years of age) which cross-reacts with striated muscle titin and RyR antigens[9].

PATHOLOGY

Thymomas are classified into 5 World Health Organization (WHO) histopathological subtypes (Table 1)[10]. Thymoma arises from thymic epithelial cells and is associated with a variable degree of T lymphocyte proliferation. These T lymphocytes are generated de novo within the thymoma from the bone marrow progenitor cells under the influence of the cortical epithelial cell-like function of the thymoma’s transformed epithelial cells. The WHO classification is based on the morphology of these epithelial cells and the amount of associated T lymphocyte, which is an indicator of the biologic function of the thymoma cells. While thymomas of WHO types A, AB, B1, B2, and B3 all show a certain amount of immature T lymphocytes, thymic carcinomas do not have a measurable number of immature T lymphocytes and are thus undifferentiated. Cortical thymoma (Type B2) is associated with MG in 50% of cases while medullary thymoma (Type A) is seldom associated with MG.

| Type | Histologic description |
|------|------------------------|
| A    | Medullary thymoma      |
| AB   | Mixed thymoma          |
| B1   | Predominantly cortical thymoma |
| B2   | Cortical thymoma       |
| B3   | Well-differentiated thymic carcinoma |
| C    | Thymic carcinoma       |

STAGING

Different staging systems are used but the most widely used system is Masaoka-Koga staging system, based on the per-operative and histopathological findings (Table 2)[11,12]. TNM staging of thymoma is not widely accepted, because it is not more useful than the Masaoka system[13].

INVESTIGATIONS

Histopathological diagnosis is the gold standard. Contrast enhanced computed tomography (CECT) thorax shows the local and regional extent of the disease. Magnetic resonance imaging aids in better soft tissue delineation and surgical planning. Routine hemogram and blood biochemistry is needed for assessing the patient’s status. Metastatic workup requires further ultrasound of the abdomen or CECT abdomen. Serum titers of antiacetyicholine receptor antibody are done to assess the myasthenia status.

TREATMENT

Surgery

Surgery is the mainstay modality for the management of thymomas. Surgery helps for exact histopathological evaluation and staging, and is the first-line treatment modality in most of the cases[14]. Immediate and complete surgical resection is advised for resectable tumors. Surgery can be approached transternally or by video assisted thoracoscopic surgery, both having similar clinical outcome[15]. Radical removal of thymoma is curative for thymic tumors in most of the cases, but patients do suffer from MG after surgery. Thus, pharmacological treatment for MG and continuous followup is necessary even after surgery. In locally advanced cases where the tumour invades pleura or pericardium, complete radical surgery is not possible and adjuvant treatment in form of radiotherapy (RT) and chemotherapy (CT) is required. Presurgical plasmapheresis or immunoglobulin (IgG) intravenous infusion helps in removal of circulating pathogenic antibodies to a significant level[16].

RT

Postoperative adjuvant RT is should be given in patients with incompletely resected tumors[17]. Stage II and
III patients after complete resection also benefit from adjuvant RT in reducing the local recurrence rates. RT doses ranging from 40 to 60 Gy is advised which includes a radiation boost to the tumor bed in incompletely resected or nonresected lesions, with a fractionation scheme of 1.8 to 2 Gy daily over a period of 4-6 wk\[18\]. Patients with poor performance status and advanced diseases with compressive symptoms are given palliative RT in doses of 30 Gy in 10 fractions or 20 Gy in five fractions.

CT
CT in thymomas is preferred in locally advanced, unresectable and metastatic disease\[18\]. The common chemotherapeutic drugs used in thymoma are cyclophosphamide, adriamycin, etoposide, ifosfamide, cisplatin (VIP)\[19,22\]. Various standard CT regimens include the following: cyclophosphamide, adriamycin, ifosfamide, cisplatin (CAP)\[19\]; cisplatin and etoposide (PE)\[20\]; adriamycin, cisplatin, vincristine, cyclophosphamide (ADOC)\[21\], and etoposide, ifosfamide, cisplatin (VIP)\[22\]. Response to CT is ranges between 32% and 92% and around 10%-43% of patients have complete responses\[23\]. Adjuvant CT has a favorable influence on survival in stage III and IV A resected thymomas. CT can be used as the initial modality in stage III and IV A unresectable thymomas\[24\]. For stage IV B thymomas with disseminated disease, CT is preferred with local RT for palliation of local symptoms\[25\].

Treatment of MG crisis in thymoma
In MG crisis, the standard management is plasmapheresis and immunoglobulin treatments\[26\]. Intense pharmacological treatment should be used along with the immunoglobulin and plasmapheresis treatment in these patients.

Pharmacological treatment of thymoma MG
The drug of choice is acetylcholinesterase inhibitors\[26\]. Immunosuppressive drugs are the second choice when additional drug treatment is required. Several immunosuppressive drugs are used, namely steroids, azathioprine, cyclosporine, tacrolimus, cyclophosphamide, methotrexate, mycophenolate mofetil and rituximab.

PROGNOSIS
Prognostic factors predicting recurrence was evaluated by Detterbeck et al\[27\] in a systemic review. The significant factors were Masaoka Stage and completeness of resection. Other factors such as age, sex, size of tumor and MG were not statistically significant in multivariate analysis.

CONCLUSION
The management of thymoma involves a multimodality approach and needs cooperation between surgeons, radiologists, pathologists and oncologists from establishing diagnosis, deciding the therapeutic strategy and evaluating the prognosis. With advances in medical science in new techniques and drugs, there is a remarkable improvement in the management of thymoma.

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