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MINIREVIEWS

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

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[2]. No sexual predilection exists. They have frequent association with various paraneoplastic syndromes (PNS)[1]. The most common PNS associated

Table 1 World Health Organization histopathological classification

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

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. Metastasic 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.

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 antiacetylcholine 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 when 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

Table 2 Masaoka-Koga staging system

Stage	Definition
I	Encapsulated tumor with no gross or microscopic invasion
II	Macroscopic invasion into the mediastinal fat or pleura or microscopic invasion into the capsule
III	Invasion of the pericardium, great vessels, or lung
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

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 cisplatin, adriamycin, etoposide, cyclophosphamide and ifosfamide. Various standard CT regimens include the following: cyclophosphamide, adriamycin, cisplatin (CAP)[19]; cisplatin and etoposide (PE)[20]; adriamycin, cisplatin, vincistine, 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[18].

Treatment of MG crisis in thymoma

In MG crisis, the standard management is plasmapheresis and immunoglobulin treatments[25]. 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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