A Middle-Aged Woman with an Anterior Mediastinal Mass and Respiratory Failure

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The discovery of an anterior mediastinal mass presents a challenge to the physician. In addition to distinguishing between benign and malignant conditions, it is important to recognize the potential for associated paraneoplastic phenomena. We present a case of a malignant thymoma associated with myasthenia gravis.

A middle-aged woman was brought to the emergency department by her family after she was found to be increasingly weak and lethargic. Earlier that day, the patient was seen at her primary care physician's office for further investigation of an "abnormal" chest radiograph obtained for evaluation of shortness of breath. The patient's shortness of breath was described as intermittent and not associated with position, activity, or exertion. Additionally, there was no associated cough, chest pain, orthopnea, or dyspnea on exertion. She also denied fever, chills, nausea, weight loss, palpitations, diarrhea, and emesis. However, it was noted that she had been experiencing intermittent periods of generalized weakness over the previous months.

The patient's past medical history was otherwise unremarkable. She was not taking any prescription medications. Her surgical history included two caesarian sections. She was married with two healthy children and worked as a cook. No history of tobacco or drug use and only occasional alcohol consumption were reported. Family history included a mother with hypertension, a father with a cerebral aneurysm complicated by a cerebrovascular accident, and a grandmother with colon cancer.

Upon examination, the patient was noted to have a fluctuating level of consciousness and associated shallow breathing. Vital signs in the emergency department revealed a temperature of 96.3°F, a blood pressure of 127/82 mmHg, a pulse of 87 beats per minute, and a respiratory rate of 8 breaths per minute. She appeared somnolent and had difficulty concentrating and answering questions. The cardiac, pulmonary, and abdominal examinations were unremarkable. The neurologic exam was normal except for decreased muscle strength bilaterally in both the upper and lower extremities.

Initial laboratory values revealed an elevated total serum protein level of 9.2 g/dL (6.3-8.0 g/dL). Basic serum chemistries and complete cell count with differential were all within the normal ranges. A urine toxicology screen detected the presence of benzodiazepines (upon further questioning, the family revealed that the

CME INFORMATION

TARGET AUDIENCE

The July/August Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, obstetricians-gynecologists, emergency medicine physicians, pediatricians, dermatologists, radiologists, and psychiatrists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be better understand the epidemiology, clinical presentation, paraneoplastic manifestations, diagnosis, and treatment of thymoma.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of 0.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Saavedra has nothing to disclose.
Dr. Culotta has nothing to disclose.
Dr. Kamboj has nothing to disclose.
Dr. Chaney has nothing to disclose.
Dr. Lopez discloses that he is a member of the *Journal of the LSMS* Board of Trustees and the *Journal* Editorial Board.

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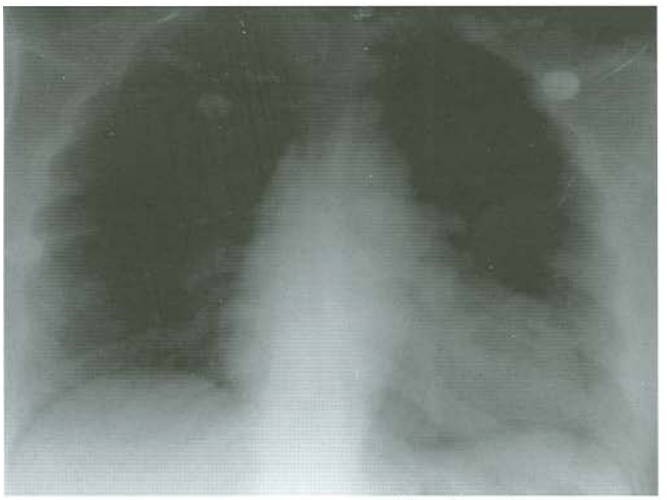

Figure 1. An anterior-posterior view of the chest demonstrating a mass-like area of consolidation in the left suprahilar region.

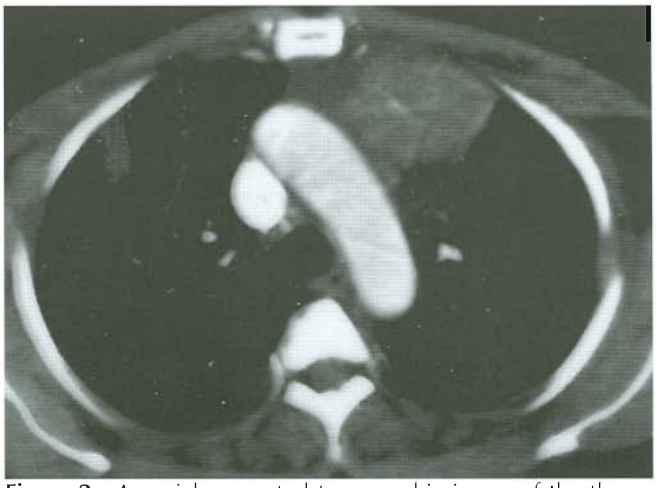

Figure 2. An axial computed tomographic image of the thorax obtained with intravenous contrast material demonstrating a 6-cm mass in the left superior mediastinum, which extends from just above the aortic arch to the level of the left main pulmonary artery. A small area of calcium deposit can be seen within the mass.

patient took alprazolam earlier in the day because of anxiety). Urinalysis revealed trace levels of protein, 1+ blood, a specific gravity of 1.030, and a few squamous epithelial cells. Initial arterial blood gas examination on air revealed a pH of 7.22 (7.35-7.45), an elevated pCO2 of 85 mmHg (35.0-45.0 mmHg), a decreased pO2 of 56mmHg (75.0-100.0 mmHg), and a serum bicarbonate of 32 mmol/L (24.0-32.0 mmol/L). A chest radiograph demonstrated a suspicious mass in the left suprahilar region (Figure 1). There was no evidence of pleural effusion, parenchymal lung disease, osseous deformities, or cardiac decompensation. A computed tomogram scan (CT) of the head revealed no abnormalities. The patient was placed on bi-level positive airway pressure and transferred to the intensive care unit for further evaluation and treatment of hypercapnic respiratory failure of unknown etiology.

After approximately 4 hours of treatment with bi-level positive airway pressure, the patient had significant improvement in her level of consciousness. A repeat arterial blood gas determination on air revealed a pH of 7.39, a pCO2 of 47.6 mmHg, and a pO2 of 62 mmHg. A CT of the chest with intravenous contrast material revealed a 6-centimeter left superior and anterior mediastinal mass extending from the level of the aortic arch to the level of the left hilum. A small focus of calcium was noted within the mass (Figure 2). Blood tests to investigate for germ cell tumors included alpha-feto protein and beta-HCG levels, both of which were within normal limits. A bone scan revealed an area of increased activity within the first left rib. The cardiothoracic surgical team was consulted for surgical evaluation and management of this anterior mediastinal mass.

The patient underwent a thorocotomy with excision of the mediastinal mass. Intraoperatively, seeding of the adjacent pericardium and part of the left upper lobe was noted. The mediastinal mass, the affected pericardium, and some of the patient's left upper lobe were resected. The frozen-section biopsy specimen demonstrated a

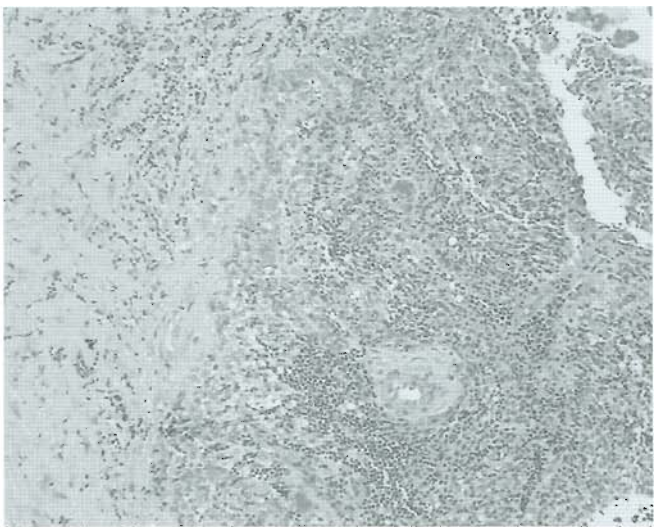

Figure 3. Histological examination of the anterior mediastinal mass showing a poorly differentiated malignant tumor consistent with a thymoma, mixed lymphocytic and epithelial type.

poorly differentiated malignant tumor consistent with a thymoma. Immunohistochemical studies of all intraoperative specimens confirmed the presence of a thymoma, mixed lymphocytic and epithelial type (Figure 3).

Acetylcholine-receptor antibody levels were found to be markedly elevated at 118.7 nmol/L (< 0.1 nmol/L). The paraneoplastic phenomenon of myasthenia gravis in association with a malignant thymoma was then postulated as the likely etiology of the patient's neuromuscular weakness and episodes of respiratory failure secondary to phrenic-nerve associated diaphragmatic weakness. The patient was started on prednisone and pyridostigmine, and referred to oncology for further evaluation and management. After approximately 3 months

of treatment with prednisone and pyridostigmine, she experienced improved strength and fewer episodes of shortness of breath. Serial acetylcholine-receptor antibody levels show document a downward trend that correlates with the improvement of her symptoms.

DISCUSSION

The thymus gland is involved in the education of T cells in early development and is replaced by fatty tissue as people age. Thymic tumors are the most common neoplastic disorders of the anterior mediastinum; they usually present during the fourth or fifth decades of life and are observed equally in men and women.[1,2] They comprise approximately 45% of tumors within this compartment bounded anteriorly by the sternum and posteriorly by the pericardium, aorta, and brachiocephalic vessels. This space is typically occupied by lymph nodes as well as the thymus gland. Other anterior mediastinal neoplasms encountered include lymphomas (second most common), germ-cell tumors, thyroid/parathyroid tumors, angiofollicular hyperplasia of lymph nodes, primary carcinomas, and mesenchymal tumors.[3] While approximately 30% of patients with thymomas may be asymptomatic, the majority of patients experience symptoms including cough, chest pain, or dyspnea.[4] Patients with more advanced disease may experience weight loss, fever, night sweats, or symptoms related to superior vena cava syndrome. The primary malignant cell line in thymomas is typically epithelial in origin. The staging of disease is based on radiographic studies as well as findings during surgical exploration. The most widely used staging system was developed by Masoka and colleagues and is based on the degree of tumor invasion into mediastinal structures.[5]

Poor outcomes may occur from mass effect, direct invasion, or distant metastasis. Paraneoplastic syndromes must also be taken into consideration in patients in whom the diagnosis of thymoma has been made or is suspected. The most common parathymic syndrome is myasthenia gravis, which occurs in approximately 30% of these patients, followed by pure red cell aplasia (2-5%), and hypogammaglobulinemia (2-5%).[6,7] In addition, approximately 10-15% of patients with myasthenia gravis will be found to have a thymoma, making the investigation of this tumor important in these patients. The physical symptoms of myasthenia gravis may include fatigable muscle weakness that does not improve with activity, ptosis, facial muscle weakness, and respiratory muscle weakness.[7,8] The disease is caused by auto-antibodies to the nicotinic acetylcholine receptors at the neuromuscular junction. The prevalence of this disease is estimated to be between 0.25 and 2 per 100,000 persons.[9] The diagnosis of myasthenia gravis can be made by detecting abnormally high serum levels of antibodies to the acetylcholine receptor or by performing the edrophonium (Tensilon) test, in which the short-acting anticholinesterase given intravenously results in a rapid, short-term improvement in the patient's muscular strength. While the association of myasthenia gravis and thymoma has been well documented, the specific immunologic mechanisms have yet to be fully elucidated.

TREATMENT

Surgical removal of all neoplastic thymic tissue is the mainstay of treatment in patients with a thymoma. In patients with non-invasive, well encapsulated (stage I) disease, the 5-year survival rate approaches 90%.[7] Adjuvant therapies with radiation and/or chemotherapy are typically reserved for patients with advanced disease. The most effective single chemotherapeutic agent is cisplatin; interleukin-2 and ifosfamide also have been used albeit with less success. [10]

The treatment of myasthenia gravis typically consists of pyridostigmine titrated to an effective dose, with the addition of corticosteroids in poorly controlled patients.[7] Intravenous immune globulin or plasma exchange may also be used when rapid improvement is desired. The beneficial effects of plasmaphoresis are seen within days of initiating treatment. The process consists of five exchange treatments of 3-4 liters over 14 days.[9] When immune globulin is used, the effective dose is usually 400mg/kg/day given over 5 consecutive days with improvement in symptoms typically occurring approximately 4 days after treatment is initiated.

CONCLUSION

Myasthenia gravis is an auto-immune disorder that may be encountered in patients with a thymoma. While these conditions may occur independently, it is critical for the physician to recognize the strong link between the two diseases. Promising treatment options exist for both conditions, but early recognition of the clinical features is important in achieving successful outcomes.

REFERENCES

1. Loehrer PJ Sr. Current approaches to the treatment of thymoma. *Ann Med* 1999; 31 Suppl 2:73-79.
2. Giaccone G. Treatment of thymoma and thymic carcinoma. *Ann of Onc* 2000; Suppl 3:245-246.
3. Hoffman OA, Gillespie DJ, Brown LR, et al. Primary mediastinal neoplasms (other than thymoma). *Mayo Clin Proc* 1993;68:880-891.
4. Wang LS, Huang MH, Chien KY, et al. Malignant thymoma. *Cancer* 1992;70:443-450.
5. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymoma with special reference to clinical stages. *Cancer* 1981;48:2485-2492.
6. Marx A, Muller-Hermelink HK, Strobel P. The role of thymomas in the development of myasthenia gravis. *Ann NY Acad Sci* 2003;998:223-236.
7. Detterbeck FC, Parsons AM. Thymic tumors. *Ann Thorac Surg* 2004;77:1860-1869.

8. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet* 2001; 357:2122-2128.
9. Drachman DB. Medical Progress: Myasthenia gravis. *N Engl J Med* 1994;330:1797-1810.
10. Sunpaweravong P, Kelly K. Treatment of thymoma: a comparative study between Thailand and the United States and a review of the literature. *Am J Clin Oncol* 2004;27:236-246.

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 223. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to August 31, 2006. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the following comments are correct *except*:
   a) Thymic tumors are the most common neoplastic disorders of the anterior mediastinum.
   b) Thymic tumors occur as frequently in men as women.
   c) Most patients with thymic tumors present during the first decade of life .
   d) The thymus gland is involved in the education of T cells.

2. True or False? Thymic tumors are the most common neoplastic disorders of the posterior mediastinum.

3. True or False? Three syndromes characteristically associated with thymoma include myasthenia gravis, red cell aplasia, and hypogammaglobulinemia.

4. All of the following statements are true *except*:
   a) Myasthenia gravis is caused by auto-antibodies to the nicotinic acetylcholine receptors at the neuromuscular junction.
   b) The physical symptoms of myasthenia gravis may include fatigable muscle weakness that does not improve with activity, ptosis, facial muscle weakness, and respiratory muscle weakness.
   c) The diagnosis of myasthenia gravis can be made by detecting abnormally high acetylcholine receptor antibody levels in serum or by performing the edrophonium (Tensilon) test, in which the short acting anticholinesterase given intravenously results in a rapid, short-term improvement in the patient's muscular strength.
   d) Though the mechanism is unknown, patients with myasthenia gravis appear to respond to oral metronidazole therapy.
   e) The treatment of myasthenia gravis typically consists of pyridostigmine titrated to an effective dose, with the addition of corticosteroids in poorly controlled patients.