

Malignant Thymoma; Educational Case with Review of Literature

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Keywords: Malignant thymoma

Abstract

Malignant thymomas are rare epithelial neoplasms of the anterior superior mediastinum that are typically invasive in nature. They have a high risk of relapse that may ultimately lead to death. They represent about 20-30% of all mediastinal tumors and 50% of anterior mediastinal masses.

Here we describe a 45-year old Sudanese female diagnosed with locally advanced malignant thymoma, treated with chemotherapy and radiotherapy

Introduction

Malignant thymomas are rare epithelial neoplasms of the anterior superior mediastinum that are typically invasive in nature, and have a high risk of relapse that may ultimately lead to death.¹ They represent about 20-30% of all mediastinal tumors and 50% of anterior mediastinal masses.² The mean age of diagnosis is 50-60 years, with no consistent gender distribution in thymoma overall.³ Management needs MDT and treatment depends on the stage and patient condition. It includes surgery, chemotherapy, and radiotherapy alone or in combination.

Case Presentation

A 45-year old Sudanese female presented with intermittent history of cough, chest pain and shortness of breath for one year prior to the diagnosis. She sought medical advice several times and was given symptomatic treatment with no improvement. She is a mother of 12 children with no significant past medical or family history. She didn't smoke and is of low socioeconomic status.

On examination, her ECOG performance status was 2, she was cachexic and dyspneic. There was a localized bulge on the left side of her chest with mild tenderness. Percussion was dull and there was impaired air entry in the upper and middle zones of the left side of the chest. Abdominal, CVS and CNS examination were all normal.

A contrast – enhanced CT scan of the chest showed a heterogeneously enhancing anterior mediastinal mass with areas of hypo attenuation suggesting necrosis, with lobulated outlines and areas of calcifications. It measured about (17.5x15 x6.5cm). The mass significantly encased the great vessels, compressed the upper part of the heart posteriorly, and to the left side. And invaded the mediastinal fat and upper and mid parts of the pericardium. On its upper left border it was not separable from the adjacent lung, but no definite lung nodules. There was a mild left side pleural effusion. No evidence of invasion into the chest wall or bone destruction. The scanned upper neck showed normal thyroid.

A core – needle biopsy was taken and the histopathology showed malignant tumor formed of sheets of cells with indistinct cell border and ovoid nuclei. No lymphoid tissue was seen. That was consistent with anaplastic malignant thymoma.

Lab investigations, echocardiography and abdominal ultrasound scan were normal. So, the patient has stage IIIB. She was given chemotherapy (cisplatin 50mg/m², adriamycin 50mg/m² and cyclophosphamide 500mg/m²) every three weeks with re evaluation after every two cycles. After four cycles, re evaluation by CT scan showed partial response, with no significant symptoms, so she was given a course of external radiotherapy, with two anteroposterior fields. A dose of 36 Gy was given by Co-60. Re evaluation after radiotherapy didn't show any further reduction in the mass, so she was not given a radiotherapy boost. Follow up and re evaluation after three months showed stable disease and no significant symptoms.

Discussion:

The WHO classification system for thymomas is based on the histologic type. Type A accounts for approximately 4-7%. Approximately 17% of cases may be associated with myasthenia gravis. The prognosis is excellent, with ≥ 15 years survival rates reported to be close to 100% in retrospective studies.⁴

Type AB accounts for approximately 28-34%. Approximately 16% of cases may be associated with myasthenia gravis. The prognosis is good, with ≥ 15 survival rates recently reported.

ed to be approximately 90% or better in 2 large retrospective studies.⁴

Type B1 accounts for approximately 9 - 20%, depending on the study cited. Approximately 57% of cases may be associated with myasthenia gravis. The prognosis is good, with 20 years survival rate of around 90%.⁴

Type B2 for approximately 20-36%, depending on the study cited. Approximately 71% of cases may be associated with myasthenia gravis. Long-term survival is decidedly worse than for thymoma types A, AB, and B1. The 20-year survival rate is on the order of 60%.⁴

Type B3 (also known as epithelial thymoma, atypical thymoma, squamoid thymoma, and well-differentiated thymic carcinoma) accounts for approximately 10-14%. Approximately 46% of cases may be associated with myasthenia gravis. The 20-year survival rate is approximately 40%.⁴

Thymic carcinoma is a thymic epithelial tumour that exhibits a definite cytologic atypia and a set of histologic features no longer specific to the thymus, but rather similar to those histologic features observed in carcinomas of other organs. The 5-year and 10-year actuarial overall survival rates are typically 38% and 28%, respectively. In contrast to the thymomas, the association of thymic carcinoma and autoimmune disease is rare.⁴

Patients with thymoma often have an indolent presentation. In other cases, the presenting clinical symptoms of these types of tumors may include cough, chest pain, and signs of upper airway congestion. Paraneoplastic syndromes associated with thymoma include myasthenia gravis, polymyositis, autoimmune pure red cell aplasia and hypogammaglobulinemia.⁵

Diagnosis is made clinically based on the radiological findings. A lateral view Chest x-ray can detect most thymomas.

CT scan of the chest delineates the lesion further and detect smaller tumors. It can also reveal features suggestive of malignancy (i.e; vascular invasion, encasement and pleural deposits).

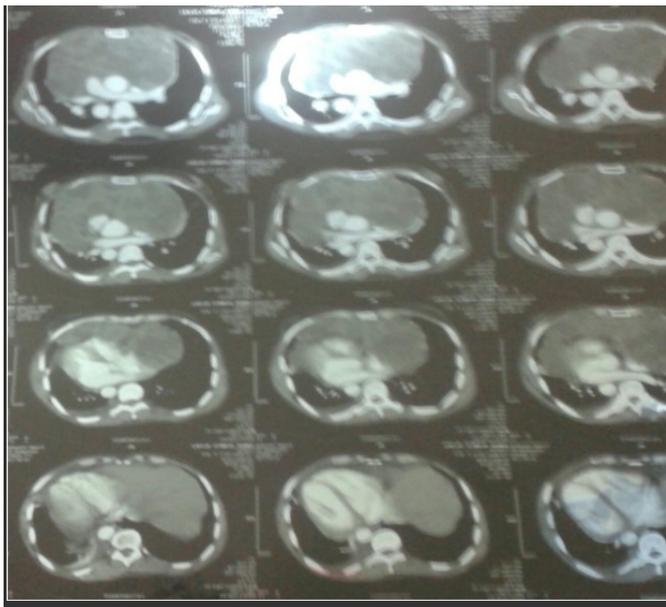
There is no standard system for staging thymoma; however, thymomas are most commonly staged according to the Masaoka system⁶.

The immunohistochemical profile of thymomas is complex due to the variety of growth patterns and background lymphoid infiltrate. Thymoma should be differentiated from other anterior mediastinal neoplasms with epithelial and/or lymphoid differentiation. NHL and Hodgkin lymphomas can be separated from thymoma by their dispersed cell population, distinctive cytologic features, and positive staining for CD45, CD20, CD15, and CD30, respectively. Mediastinal seminomas are immunoreactive for PLAP and CD117, while CD30 is expressed in 85–100% of embryonal carcinomas. Similar to thymomas, mediastinal neuroendocrine neoplasms express CD57 and other neuroendocrine markers but are consistently negative for non-neoplastic immature lymphocytes (CD1a+, CD99+).⁷

It is sometimes difficult to make the differential diagnosis between thymoma type B3 and thymic carcinoma histologically, especially when the biopsy specimen is small. Immunoreactivity for CD5 and c-kit has been reported as a useful marker for primary thymic carcinoma, but not for thymoma, some data showed that CD5 expression is of limited value in the differential diagnosis since both thymic carcinomas and thymomas may express CD5⁸. A study by Masakazu Kojika et al showed that the seven markers selected, that is, GLUT-1, CA-IX, c-kit, CD5, MUC-1, CEA, and CK18, were useful for differentiating between type B3 thymoma and thymic carcinoma.⁹

All patients with thymic malignancies should be evaluated in multidisciplinary meeting by a radiation oncologists, medical oncologists, thoracic surgeons, radiologists and pulmonologists to determine the optimal plan of treatment¹⁰ that depends upon the stage, pathology and extent of disease and includes a combination of surgical resection, chemotherapy, and radiotherapy. If the lesion is resectable, then total thymectomy with complete excision of the tumor is the standard treatment,^{11,12} Most thymomas present with stage one, which is treated by surgery and has a good prognosis. For locally advanced disease, induction chemotherapy with or without radiotherapy is recommended.¹³ It is known that most thymic tumours are chemo- and radio-sensitive.¹⁴ Induction chemotherapy has been successfully used to down-stage unresectable tumors for surgical resection and to prevent local and systemic recurrences. Various case series and small prospective trials have shown the clinical effectiveness of chemotherapy in the management of advanced malignant thymomas. Cisplatin -based combination chemotherapy with doxorubicin, cyclophosphamide, ifosfamide or etoposide is effective against thymic tumors.^{15,16}

In a Japanese series of 1320 patients with stage III and IV



thymoma, the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 93%, 64%, and 36%, respectively.¹⁷ In addition to total thymectomy inspection of the pleural surfaces with resection of any visible pleural metastasis should be performed.¹⁸

An MD Anderson a study of 12 patients treated with induction chemotherapy, 3 cycles of cyclophosphamide, cisplatin and prednisolone, followed by surgery and postoperative radiotherapy followed by 3 similar cycles of chemotherapy, 25% had a complete response, 67% had a partial response, and 8% had a minimum response, all the 12 patients were alive 7 years.¹⁹

Some prospective studies included 111 patients treated with variable chemotherapy regimens, including octreotide, cisplatin, etoposide, ifosfamide and others. Overall response rate was 32-56%, complete response 13-38%, 2 years overall survival 30-79%, and progression free survival 13-56 %.²⁰⁻²²

Little has been reported on the role of radiation therapy in the management of malignant thymoma. A case report showed results that 40 Gy/20 fractions is probably the minimum recommended dose for local control with Co⁶⁰ or Lineac. Larger or unresectable tumors should receive 45-48 Gy in five to six weeks.²³ ESMO guidelines recommend 45-50 Gy after complete resection, 50-54 Gy if incomplete resection and 60 Gy for definitive radiotherapy.³

Our patient was treated with 4 cycles of chemotherapy with partial response. Then received EBRT 36Gy/20 fractions. No radiation boost given as the mass didn't respond to EBRT. Three months after that the patient is well with no significant symptoms.

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