Management of Advanced Thymoma Presenting with Myasthenia Gravis in a Resource-limited Setting: A Case Report

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ABSTRACT

Thymomas are rare tumours which generally account for only 0.2 – 1.5% of mediastinal tumours in adults. Around 40% of patients present with systemic symptoms such as motor weakness due to myasthenia gravis (MG), pure red cell aplasia, and hypogammaglobulinemia. Based on recent guidelines, management of advanced thymoma uses a multimodal approach, which is thymectomy followed by radiotherapy, but not all health care centers have radiotherapy facilities.

A 52-year-old woman presented with nasal voice and had difficulty swallowing food. Patient was diagnosed with myasthenia gravis (MG). CT scan with contrast of the thorax showed a heterogenous solid mass in anterior mediastinum. Histopathological examination showed thymoma type B2. Thymectomy followed by seven cycles of platinum-based chemotherapy were done on the patient. Evaluation afterward showed complete remission of thymoma. The patient's motor weakness improved after the chemotherapy. Post-chemotherapy period was uneventful at six months on follow-up visit. The dosage of acetylcholinesterase inhibitor drug is reduced periodically due to improvement in motor weakness.

The case emphasizes how to manage an advanced thymoma with MG with limited therapeutic options, and the importance of multidisciplinary management involving oncologists, surgeons, and neurologists.

Keywords: thymoma, myasthenia gravis, chemotherapy, thymectomy, case report

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INTRODUCTION

Thymoma is a neoplasm that generally originates from thymic epithelial cells. The thymus is most active and reaches its largest size during childhood, then it shrinks and atrophies in late adolescence. Despite atrophic condition, lymphopoiesis of T cells persists into adulthood.[1] Thymoma is classified into several subtypes by the World Health Organization (WHO) based on the morphology of the tumour cells and the proportion of immature T cells, namely type A, A atypical, AB, B1, B2, B3, MNT, and metaplastic thymoma.[2]

Thymomas are rare tumours which generally account for only 0.2 – 1.5% of mediastinal tumours in adults.[1] In Europe, the incidence of thymoma is 1.7 million per year.[3] Thymomas can occur at any age, but the peak age ranges from 35 to 70 years.[4] The incidence of thymoma increases from 3% at age 20 to 21% at age 21 to 45 years.[1]

About 30% of thymoma is asymptomatic and discovered accidentally, but some patients have local symptoms such as chest pain, coughing, and shortness of breath. In large

thymoma, it can cause superior vena cava syndrome.[4] Around 40% of patients present with systemic symptoms such as motor weakness due to myasthenia gravis (MG), pure red cell aplasia, and hypogammaglobulinemia. Myasthenia gravis is a neuromuscular junction disease which is characterized by muscle weakness caused by autoantibodies.[5] The most common autoantibodies found in thymoma are antibodies against the acetylcholine receptor (AChR).[5–7]

Based on recent guidelines, management of advanced thymoma uses a multimodal approach, which is thymectomy and continued with radiotherapy.[3] Thymectomy is indicated in all cases with thymomas.[8] Chemotherapy is usually performed preoperatively on unresectable thymoma.[9] Chemotherapy has a fairly good effectiveness against thymoma with *overall response rate* (ORR) of 92%, suggesting it as an alternative treatment after thymectomy, especially in limited-resource setting.[10,11]

In recent guidelines, thymectomy is the main treatment followed with radiotherapy if complete resection cannot be achieved. We present an advanced stage thymoma that is successfully treated with thymectomy followed by chemotherapy. The aim of this case report is to present our experience in managing advanced stage thymoma with MG with limited treatment options.

CASE REPORT

A 52-year-old woman presented with nasal voice and had difficulty swallowing food in the last eight months. There were no other complaints such as double vision and difficulty in closing eyes, speaking, chewing, breathing, and moving the neck or extremities. Urination and defecation were normal. The patient was diagnosed with MG three months prior and was taking pyridostigmine 60 mg-30 mg-30 mg-60 mg orally. Repetitive nerve stimulation test was done to the patient and resulted to positive decrement test. Complaints felt better with medication. The patient had thymectomy one month ago. Patient denied any history of similar disease in the family. The patient previously worked as a farmer, but is currently not working.

On physical examination, patient was mentally sound and has normal vital signs (blood pressure - 120/80 mmHg, pulse rate - 84 bpm, respiration rate - 16 bpm with 99% oxygen saturation, and temperature of 36.5°C). The patient's weight is 29 kg with a height of 142 cm [body mass index (BMI) is 14.48 kg/m^2 underweight]. The patient's body surface area is 1.07 m^2. There were no ptosis nor palpable enlarged lymph nodes. There was a surgical wound on the thoracic area. Pulmonary and cardiac physical examination were normal. Patient had normal motor strength in four extremities.

Chest x-ray showed a well-defined opacity, projected at the level of the left 4-6 thoracic vertebrae, forming an obtuse angle to the mediastinum, suspected of mediastinal mass (Figure 1). Contrast-enhanced computed tomography was done which suggested a mediastinal anterior mass originating from the thymus with size of ± 6.3 x 3.9 x 8.3 cm. The mass was attached to a part of the aortic arch, visceral pleura, and anterior aspect of the parietal pericardium. There were multiple lymphadenopathies on the right and left supraclavicular areas, right upper-lower paratrachea, left hilum, and right and left axillae with the largest size ± 1.5 x 1.3 cm in the right upper paratracheal (Figure 2). Patient had thymoma stage IVB. She was medically managed with oral pyridostigmine 60mg-30 mg-30mg-60mg daily. Thymectomy was done. Histopathological examination of thymoma showed lymphoid cell proliferation (predominantly mature lymphocytes) with round-oval cell morphology, round-oval nuclei, mild nuclear pleomorphic, with vesicular nuclei in between. These cells appear to be scattered in single

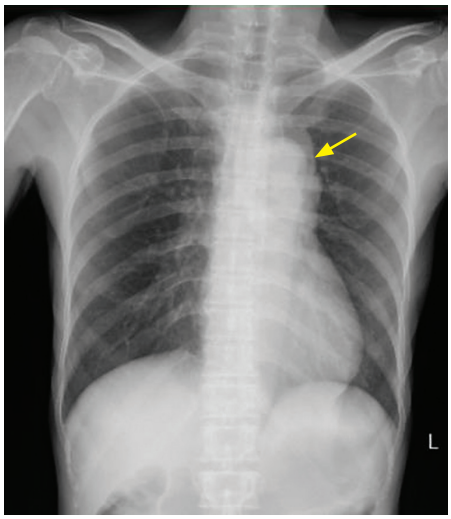

Figure 1. Chest x-ray showing mediastinal anterior mass *(yellow arrow)*.

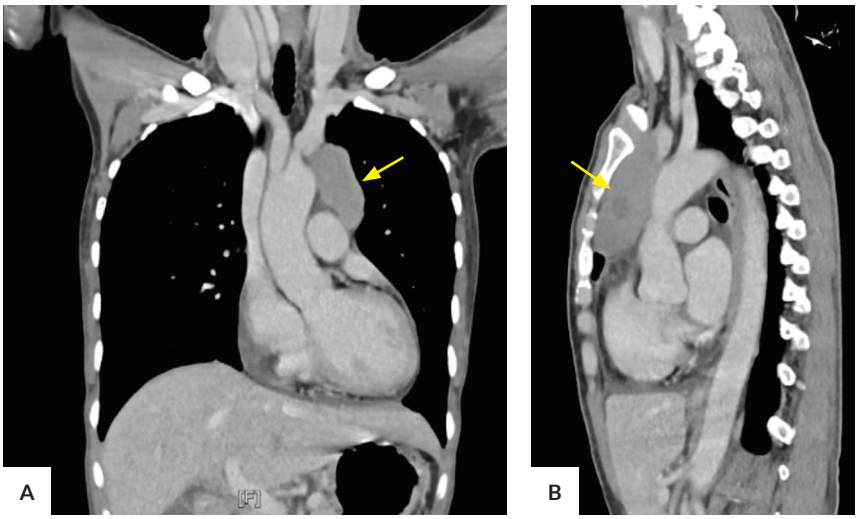

Figure 2. CT scan showing mediastinal anterior mass *(yellow arrows)*.

cell and cell cluster patterns (>3 cells) (Figure 3). It is in accordance with thymoma type B2. On examination, it was found that some of the edges of the tissue still contained tumour cells.

After thymectomy, the patient was given a platinum-based chemotherapy (ADOC regimen). The ADOC regimen consisted of doxorubicin 40 mg/m^2 (42.8 mg) which was given in 3-5 minutes on the first day, cisplatin 50 mg/m^2 (53.5 mg) in 50–250 cc 0.9% NaCl which was given in one hour on the first day accompanied by hydration of 1000 cc 0.9% NaCl which was given in 2-4 hours before and after administration of cisplatin, vincristine 0.6 mg/m^2 (0.64 mg) which was given in 1-2 minutes on the second day, and cyclophosphamide 750 mg/m^2 (749 mg) in 5-150 cc of 0.9% NaCl which was given in 15 minutes on the fourth day. The chemotherapy cycles were given every 21 days.

After four series of chemotherapy, contrast-enhanced tomography was done and no residual masses were seen with multiple subcentimeter lymphadenopathy (<1 cm) in the right and left supraclavicular areas, right upper paratrachea, and right and left axillae (RECIST 1.1 complete response) (Figure 4A). Chemotherapy was continued until the seventh series.

After thymectomy, patient still felt the weakness persisted, as it was difficult for her to swallow hard food. During chemotherapy session, patient felt relieved that her

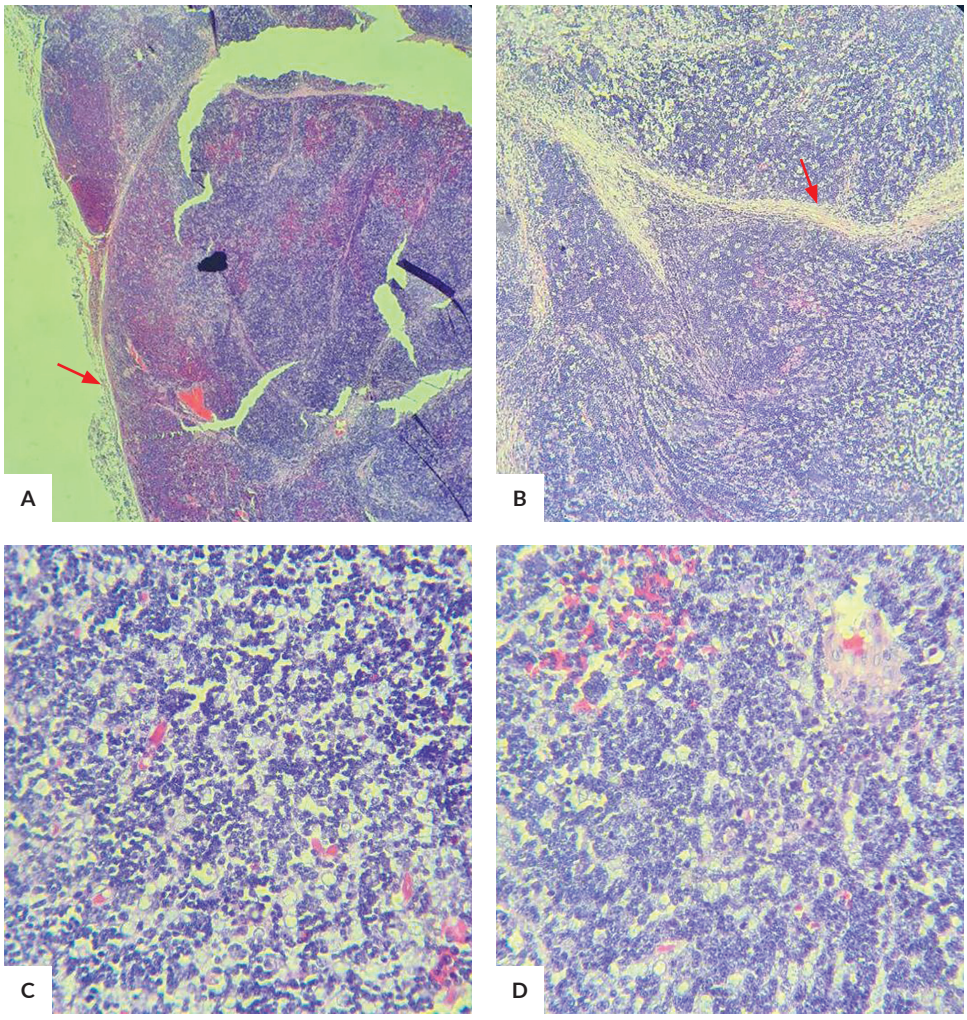

Figure 3. ***Histopathological Examination.*** **(A)** Well demarcated, lobulated tumor mass, partially covered by a connective tissue capsule *(red arrow)* (HE, 40x); **(B)** Lobulated tumour mass circumscribed by fibrous connective tissue septa *(red arrow)* (HE400x); **(C)** Proliferation of lymphoid cells (predominantly mature lymphocytes) was seen with round-oval cell morphology, round-oval nuclei, mild nuclear pleomorphic, with vesicular nuclei in between (HE,400x); **(D)** Cells appear scattered in a single cell and cell cluster pattern (>3 cells) among mature lymphocytes. Mitoses are hard to find (HE, 400x).

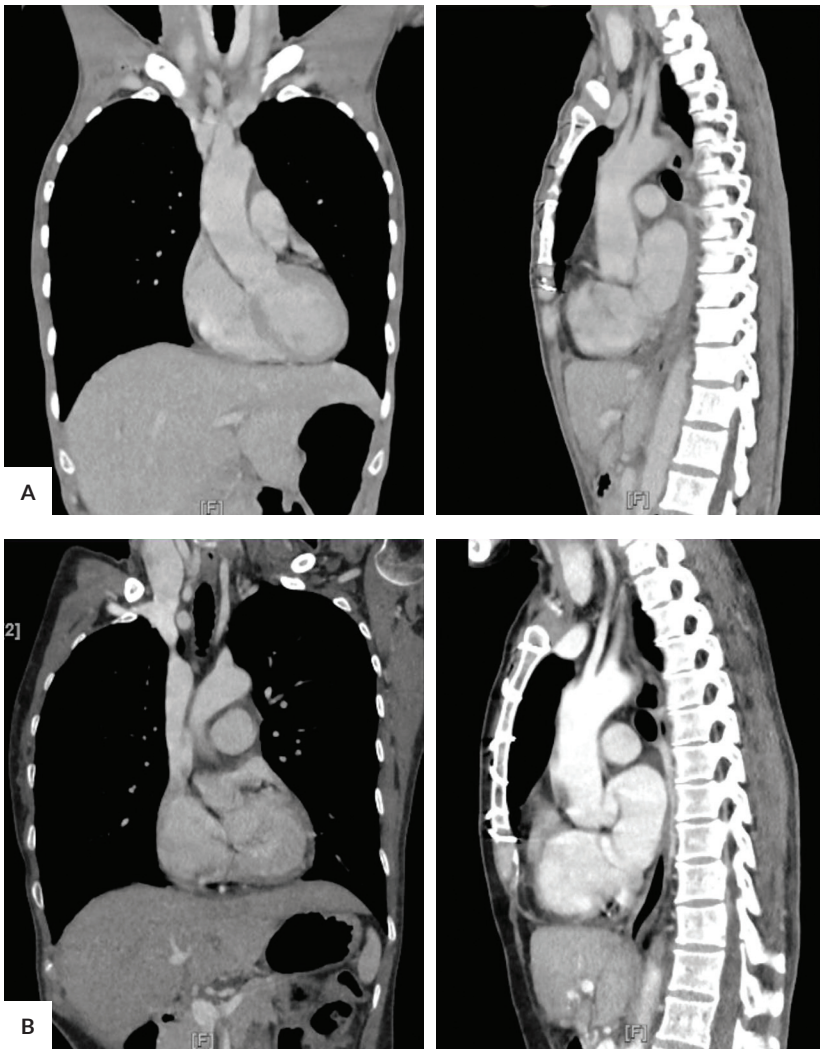

Figure 4. CT scan showing **(A)** Complete remission after four series of chemotherapy; **(B)** No recurrence after six months on follow-up.

symptoms were gradually getting better. Difficulty swallowing and nasal voice improved. The patient denied any shortness of breath. The dosage of pyridostigmine was reduced to 60 mg every 8 hours orally. Six months after seven series of chemotherapy, no mass was seen on the CT scan (Figure 4B). Patient complained of mild nausea after chemotherapy that was manageable with anti-emetic drugs.

DISCUSSION

The peak age of thymoma and MG is 35-70 years and 30-60 years, respectively.[4] Epithelial tumours of the thymus are extremely rare, with an estimated 1000 cases per year in Europe. The survival rate for thymoma has increased, from 81% to 85% at one year and 58% to 65% at five years. There is no difference in survival in women and men. Survival in the age group less than 25 years is 78%, 72% in the 25-64-year group, and 60% in the age group 65 years and over.[3]

About 30% of thymoma are asymptomatic, but about 40% of patients have local symptoms, such as chest pain, cough, shortness of breath, dysphagia, and superior vena cava syndrome.[9] About 40% of patients have systemic symptoms, such as MG, pure red cell aplasia, adenoma parathyroid, and hypogammaglobulinemia.[3,4] About 25-45% of thymoma patients have MG.[9] Patient came with motor weakness due to MG.

The type of thymoma that most often causes MG is thymoma type B, also called the cortical type.[7] Cortical thymoma has the ability of normal thymoma cortex, which can cause maturation of immature T cells into mature T cells thereby increasing the number of mature T cells in the periphery.[12] In addition to increasing immune cells, thymoma can express epitopes that resemble protein in skeletal muscle, such as acetylcholine receptor (AchR), titin, and ryanodine receptor (RyR). These epitopes are presented to T cells causing the formation of antibodies specific to these proteins.[7]

Apart from that, genetics plays a role, where patients with HLA-DR3 are more at risk of experiencing late-onset MG (onset >50 years).[13]

Eighty-five percent of MG patients have AChR antibodies.[7] AChR antibodies are the main antibody to MG in thymoma, but non-AChR antibodies such as antibodies to titin and RyR also play an important role.[14] Titin is a protein in the sarcomere that is useful for muscle contraction, so interference with this protein will cause muscle weakness.[15] Ryanodine receptor is a calcium channel on the sarcoplasmic reticulum. The function of RyR is when it opens, it causes the release of calcium into the sarcoplasm and causes muscle contraction. Antibodies against RyR will inhibit the release of calcium into the sarcoplasmic reticulum by causing muscle weakness.[16]

Treatment of thymoma can be divided into thymectomy and systemic therapy, such as chemotherapy and radiotherapy. If possible, all thymoma need to be completely resected because there is a possibility of malignancy.[4] The goal of surgery is complete resection of the tumour, thymus and perithymic fat.[2] The need for radiotherapy after surgery will be determined by whether a complete resection can be performed, the stage, and the histological examination results. In patients with WHO stage I and II thymoma types A, AB, and B1, radiotherapy post-operative is not necessary, because it has not been proven useful. In patients with higher stages and/or WHO types B2, B3, and C, radiotherapy is highly advised.[3]

Combination chemotherapy was popular in the 1980s and early 1990s.[11] Adjuvant chemotherapy is given with the aim to reduce the chance of recurrence and metastasis, hence prolong survival. Thymic cancer and advanced thymoma are rare and there is no standardised dose and cycle of chemotherapy should be given.[17] The combination chemotherapy that is generally used is platinum-based chemotherapy, namely the CAP regimen, CAP with prednisone, ADOC regimen, PE regimen, and etoposide/ifosfamide/cisplatin.[18] ADOC regimen (cisplatin 50 mg/m^2 the first day, doxorubicin 40 mg/m^2 the first day, vincristine 0.6 mg/m^2 the third day, and cyclophosphamide 700 mg/m^2 the fourth day every three weeks) has comparable result with an ORR of 92% and an overall survival (OS) of 15 months.[10,11,17]

In this patient, thymectomy was performed, followed by chemotherapy. After four series of chemotherapy, patient had complete response, with no residual mass and subcentimeter lymphadenopathies.[19] Due to high recurrence rate of advanced thymoma and our experience, we advised the patient to do chemotherapy until seven cycles. Five months after chemotherapy, patient did not show any sign of recurrent thymoma.

Recurrence of thymoma stage I, II, and III are 3%, 15% and 26%, respectively. The average recurrence time is 10 years for stage I and three years for stages II-IV. Factors associated with lower recurrence are stage I and II, complete resection, and smaller size.[4] Patients should have CT scan of the thorax every six months for the first two years, then annually every five or ten years. This is because the recurrence rate is quite high.[3] The patient had a chest CT scan after six months on follow-up and showed no signs of recurrence.

Tumor stage is an important factor in determining the patient's prognosis. The 5-year survival of completely resected patients for stage I, II, III, and IV were 90%, 90%, 60% and 25%, respectively. Histopathological subtype is important. Type A, AB, and B1 have overall survival of 90% to 95% at 10 years. Other factors lowering patient's prognosis were incomplete resection, MG, early recurrence, and age more than 40 years old.[3]

Our case was followed-up six months after seven series of chemotherapy. She was satisfied with her improvement. With high recurrence rate, longer follow-up period is better. Further studies are still needed to generalize the usage of chemotherapy in advanced case of thymoma. Limitation of this case report is lack of modalities to assess the response of therapy. Other modalities such as PET-Scan can provide better evaluation.

This patient has complete response to chemotherapy after thymectomy. This showed that chemotherapy can be used instead of radiotherapy in patients with advanced stage of thymoma who had incomplete resection, even in thymoma type B2.

CONCLUSION

Treatment of advanced stage thymoma with myasthenia gravis using thymectomy followed with platinum-based chemotherapy showed promising results. After the treatment, patient had complete remission with improvement in motor weakness.

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Statement of Authorship

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Author Disclosure

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