Myasthenia Gravis with Mediastinal Tumors

Alfansuri Kadri(✉) and Utami Tarigan

Department of Neurology, Faculty of Medicine, University of North Sumatera, Medan, Indonesia
alfansurikadri@yahoo.com

Abstract. Introduction: Myasthenia Gravis (MG) is an autoimmune disease caused by antibodies targeting acetylcholine receptors to reduce the depolarization ability of extraocular, bulbar, and proximal muscles. Mediastinal tumors associated with MG are known as paraneoplastic syndromes and are primarily found in the anterior compartment, consisting of thymoma, lymphoma, and germ cell tumors.

Case Report: Two cases of MG with mediastinal tumors came for examination at H. Adam Malik General Hospital (RSUP HAM), Medan. Each of these cases has a different clinical presentation and symptoms. In the first case, MG with thymoma presented symptoms of ptosis, diplopia, dysphagia, dysphonia, and dropped head. The second case was MG with Primary Mediastinal Large B Cell Non-Hodgkin Lymphoma with symptoms of dysphonia and dysphagia. The patients were subjected to different treatments and experienced significant clinical improvement.

Discussion and Conclusion: The diagnosis of mediastinal tumors was established based on clinical symptoms, neurological examination, and investigations. The first case was managed using acetylcholinesterase inhibitors, steroids, non-steroidal immunosuppressants, and thymectomy, while the second utilized acetylcholinesterase inhibitors, steroid immunosuppressants, and radiotherapy.

Keywords: Myasthenia Gravis · Mediastinal Tumor · Paraneoplastic syndrome

1 Introduction

Myasthenia gravis (MG) is an autoimmune disorder affecting the skeletal muscles' neuromuscular junction (NMJ). The classical presentation is a fluctuating weakness of the eyes, throat, and extremities muscles, worsening with exertion and improving with rest [1, 2]. MG is an autoimmune B-cell mediated disease which correlates with the presence of antibodies against the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), agrin, titin, and ryanodine in the postsynaptic membrane at the NMJ. It is classified into seven subtypes, including early-onset, late-onset, thymoma, MuSK, LRP4, seronegative, and ocular MG, based on the mechanism of autoimmune disease and antibodies, invasive skeletal muscle molecules, thymus status, genetic characteristics, disease phenotype, and response to treatment [3, 4]. The patients with thymoma have detectable AChR and additional

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paraneoplasia-associated antibodies including antivoltage-gated K+ and Ca++ channels, anti-Hu, antidihydropyrimidinase-related protein 5, which are anti-glutamic acid decarboxylase [2].

Mediastinal tumors are located within the mediastinum, between the right and left lungs, consisting of thymoma, lymphoma, and germ cell. Furthermore, it may be associated with compression or invasion of adjacent structures, leading to severe lifethreatening emergencies. These tumors may be characterized by non-localized symptoms caused by paraneoplastic neurologic disease (PND). The disorder is not related to tissue invasion by tumors, distant metastases, or metabolic side effects/toxic effects of cancer therapy. However, it is triggered by the response of autoimmune resistance to antigens that are co-expressed with tumors and target organs, such as the nervous system and muscle tissue. Mediastinal tumors are associated with MG through a possible mechanism known as paraneoplastic syndrome [5–8].

2 Case I

A 37 years old woman came to H. Adam Malik Hospital Medan with a chief complaint of difficulty lifting the eyelids one and half months before admission to the hospital. The difficulty was initially felt in the right eyelid after fatigue. These problems fluctuated, appeared and worsened more frequently with physical activity, diminished and returned to normal at rest. The complaint worsened until the right eyelid closed, followed by the left and accompanied by nasal sounds with difficulty swallowing. The patient was subjected to treatment and EMG examination in Medan with positive Harvey Masland test 10 days before coming to the hospital. Furthermore, the diagnosis was conducted and treated with Mestinon 3 × 60 mg and Prednisone 3 × 5 mg. The patient was subjected to further examination at H. Adam Malik Hospital for CT thoracic scan because of no significant improvement. Neurological examination showed symptoms such as ptosis, diplopia, dysphonia, dysphagia, and dropped head. Meanwhile, wartenberg, ice-packed, and single breath counting tests were positive. Repetitive Nerve Stimulation was also conducted, and CT thoracic scan showed mediastinal tumor dd thymoma. The patient was subjected to sternotomy surgery + mediastinal tumor resection before histopathology examination, which showed thymoma sinistra with a frequency of 3, 5, 7, 10 Hz pre and post-exercise, decrement > 10% was not found. Stimulation M.trapezius (N. Accessorius) dextra with a frequency of 3, 5, 7, 10 Hz pre and postexercise, decrement > 10% was found. Impression: Harvey Masland's test was positive (Figs. 1 and 2).

3 Case II

A 26 years old woman came to H. Adam Malik Hospital Medan with the chief complaints of hoarseness and difficulty swallowing for 2 months before admission to the hospital. These symptoms fluctuated, and hoarseness occurred when speaking frequently. Furthermore, the hoarseness diminished or vanished after resting or waking up in the morning. The patient felt difficulty swallowing, especially when drinking, and previously received Mestinon 2 × 60 mg from another hospital 3 days before admission. The patient had experienced shortness of breath 3 months before admission. It worsened during activities

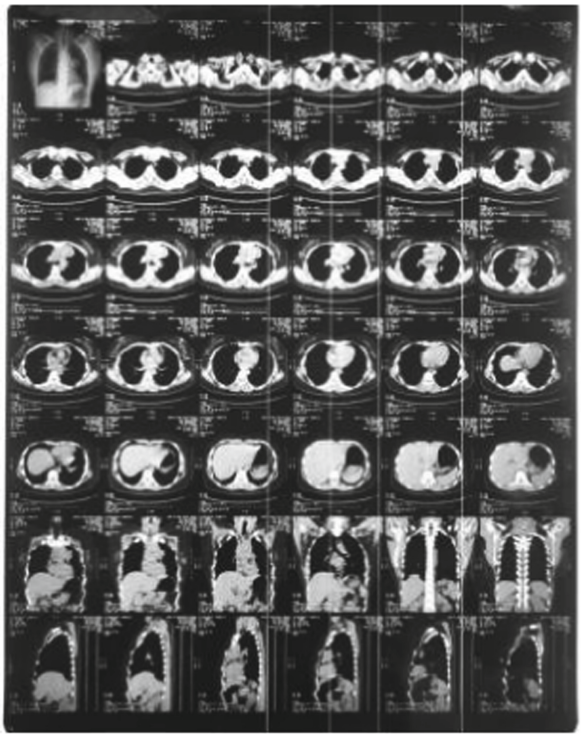

Fig. 1. Thoracic CT scan without contrast showed a well-defined lobulated tumor mass in the superior anterior mediastinum measuring 8 × 4 × 4.5 cm. Density looked heterogeneous, with lobulated edges with microcalcification components. The boundary between the tumor and the surrounding mediastinal vascular was visible, corresponding to thymoma appearance.

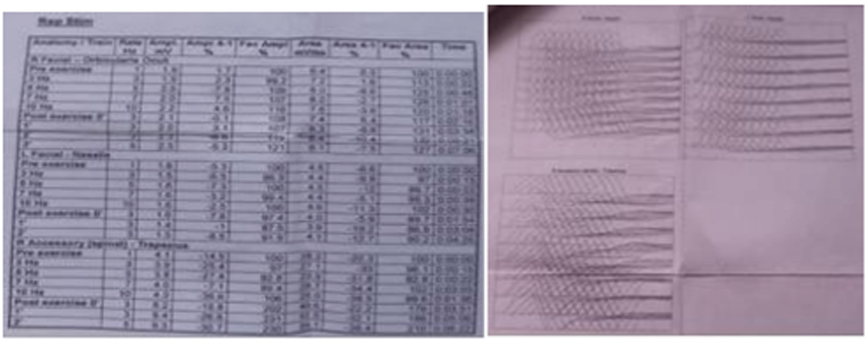

Fig. 2. Stimulation M.orbicularis oculi (N.Fascialis) dextra with a frequency of 3,5,7,10 Hz pre and post-exercise, decrement > 10% was not found. Stimulation of M. nasalis (N. Fascialis) sinistra with a frequency of 3,5,7,10 Hz pre and post-exercise, decrement >10% was not found. Stimulation M.trapezius (N. Accessorius) dextra with a frequency of 3,5,7,10 Hz pre and post-exercise, decrement >10% was found. Impression: Harvey Masland's test was positive.

and decreased at rest. Additionally, shortness of breath was associated with the patient's position when lying down. Since three months ago, the patient's cough has been accompanied by white phlegm, and a stabbing left chest pain that has intensified over time. In 3 months, 5 kg of weight loss was reported. Physical examination found dim percussion in the upper field to the bottom of the left lung and weak sounds in the upper and lower fields. Neurological examination found dysphagia and dysphonia, and a single breath counting test showed a positive result, with a disappearing voice on a count of 10. The patient was previously treated in an outside hospital with mediastinal tumors. There was a history of chest tube insertion, transthoracic needle aspiration (TTNA), and core biopsy. The complaints worsened, and the patient had signs of vena cava superior syndrome. Cytoradiotherapy was provided, a favorable response was observed, and radiation was repeated up to ten times. The patient was also subjected to a repetitive examination nerve stimulation (RNS) with a positive Harvey Masland test and diagnosed with MG before treating with Mestinon 3 × 60 mg. Histopathological examination showed the cytological effects of a primary mediastinal large B cell non-Hodgkin lymphoma, DD: Mediastinal Seminoma. Immunohistochemical examination showed nonHodgkin lymphoma and diffuse Large B-cell Lymphoma (DLBCL). During the treatment on the ward for about 2 weeks, the general condition gradually improved. The patient was discharged and continued chemotherapy and pulmonary polyclinic treatment (Figs. 3 and 4).

4 Discussion

In this study, two cases of MG were presented with mediastinal tumors. In the first case, a 37 years old woman came to H. Adam Malik Hospital Medan with a chief complaint of difficulty lifting her eyelids one and half months before admission to the hospital. The difficulty of lifting the eyelids was initially felt in the right eyelid after fatigue. These problems fluctuated, appeared and worsened frequently with physical activity, diminished and returned to normal at rest. This complaint worsened until the right eyelid closed, followed by the left and nasal sounds with difficulty swallowing. Neurological examination showed ocular symptoms such as ptosis and diplopia, bulbar symptoms such as dysphonia and dysphagia, and dropped head. This patient was classified as having generalized early-onset myasthenia gravis based on age onset [9]. The patient was treated to control symptoms with acetylcholinesterase inhibitor pyridostigmine. Pyridostigmine is the initial therapy of MG, with rapid onset of action (15–30 min) and peak activity within 2 h. An initial dose of pyridostigmine bromide is 30–60 mg every 4–6 h and can be titrated according to the response. Pyridostigmine is taken 30–60 min before meals in patients with bulbar symptoms. The dose can be increased and adjusted according to clinical response and side effects.9 Therapy response with pyridostigmine in this patient was adequate initially, and the patient improved after taking the drug a few hours later.

Over time, the patient's symptoms worsened, and treatment with pyridostigmine had not obtained satisfactory results, even with an increasing dose. The patient was treated using an additional steroid immunosuppressant and prednisone with an initial dose of 3 × 5 mg. The therapy response of immunotherapy in early-onset MG showed good outcomes. It can prevent the worsening of MG symptoms at the initiation of therapy. The initial dose is equivalent to 10–20 mg/day of prednisone, increasing the dose weekly

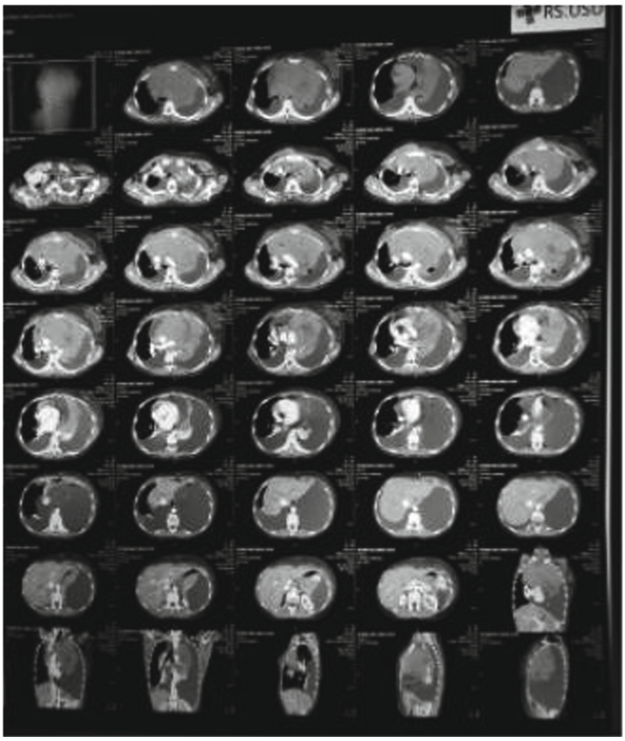

Fig. 3. Thoracic CT scan with contrast IV showed Irregular solid dominant mass, with malignant characteristics, in the mediastinum superior and anterior medial left dominant, attached to the trunk of the pulmonary aorta, superior vena cava, and pleura in that area, and compressed the left main bronchus. Left pleural effusion. CT-Scan

to 5 mg/day until stable clinical improvement is achieved. The duration of action can last up to 18 months, with an average of 3, and response will appear within 2–3 weeks after initiation of therapy. On the first day of glucocorticoid therapy, there is often a transient worsening of myasthenic symptoms, especially in patients with severe bulbar palsy. Some experienced a temporary worsening of high doses of prednisolone at the initiation of therapy. This worsening occurs after 4–10 days of treatment and can trigger an MG crisis [9, 10].

MG symptoms did not immediately improve or worsen after a few weeks of steroid use, and the condition was stable. In a retrospective study, glucocorticosteroids, prednisone, prednisolone, and methylprednisolone, had shown the ability to improve clinical symptoms in several weeks to months (mean 4–8 weeks) in 70–80% of patients. Due to side effects, long-term oral glucocorticoids are combined with steroid-sparing immunosuppressive drugs, such as azathioprine. In cases when a long-term immuno-suppressant is necessary, azathioprine is advised, and the steroid dose is adjusted to be as low as possible (Level recommendation A) [9].

In this patient, azathioprine immunosuppressive medication was added. This drug takes longer, and the therapeutic effect will appear in the patient's body when the steroid

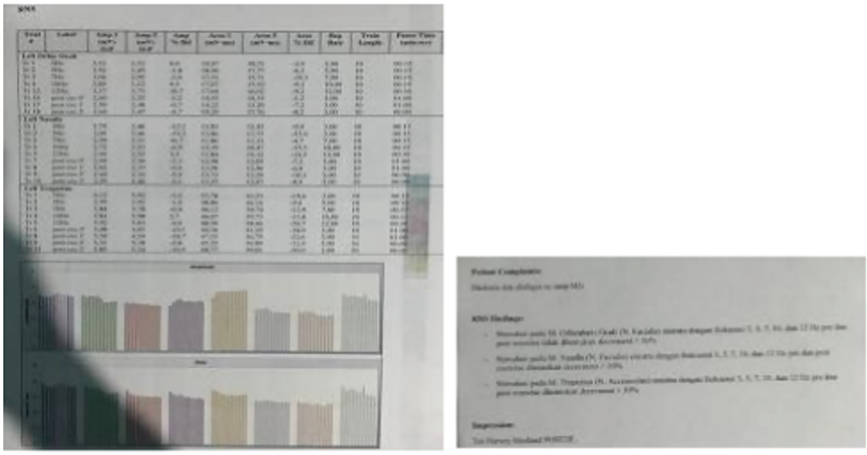

Fig. 4. Stimulation M.Orbicularis oculi (N.Fascialis) dextra with a frequency of 3,5,7,10 Hz pre and post-exercise, decrement > 10% was not found. Pre and post-stimulation of M. nasalis (N.Fascialis) sinistra and M.trapezius (N. Accessorius) dextra with a frequency of 3,5,7,10 Hz resulted in decrement >10%, indicating a positive Harvey Masland's test.

dose is 4–12 months, with a maximum effect achieved after 6–24 months of treatment. Some research demonstrated the efficacy of better outcomes in patients with a combination of azathioprine and steroid (level of evidence class I). Long-term use of azathioprine in combination with steroids is recommended in patients requiring long-term immunosuppressant drugs. Steroid reduction is titrated at the lowest possible dose while maintaining the azathioprine (recommended level A) [5].

The patient was subjected to CT thoracic examination and showed the presence of an anterior mediastinal tumor with a thymoma impression. Significant clinical improvement was noticed after the thymectomy was performed. The MG composite score decreased from the highest, 17 before surgery, to 0, two weeks after thymectomy. This indicated that complaints, such as ptosis, diplopia, dysphonia, dysphagia, and drop head, were no longer appearing. Titrated steroids conducted the treatment in a stable condition within 1 month. The patient showed excellent response in the early onset MG with thymoma. Thymectomy could be a good therapy option performed within 1–2 years of diagnosis. The main goal is significantly to improve weakness and reduce the drug dose. Some experts believed a large number of remission after surgery was between 20–40% depending on the type of thymectomy performed. Other experts believe that remission depends on the number of extensive procedures between 40–60% five to ten years after surgery [11]. In general, most patients experience improvement within one year after thymectomy, and not a few show permanent remission.

In the second case, a 26 years old woman came to H. Adam. Hospital Malik Medan, with complaints of hoarseness and difficulty swallowing. The patient experienced this hoarseness for 2 months before admission to the hospital. These symptoms fluctuated, hoarseness occurred when speaking frequently, and hoarseness diminished or vanished after resting or waking up in the morning. The patient felt difficulty swallowing, especially when drinking, and experienced shortness of breath 3 months before admission.

Furthermore, breathlessness was also associated with the position of lying down. The patient complained of a cough and stabbing chest pain with a 5 kg weight loss in 3 months. Physical examination found dim percussion in the upper field to the bottom of the left lung and weak sounds in the upper and lower fields. Neurological examination found dysphagia and dysphonia, and a single breath counting test showed a positive result with a disappearing voice on a count of 10.

The patient was subjected to repetitive nerve stimulation (RNS) examination with positive Harvey Masland's and was diagnosed with MG. The CT thoracic scan showed an irregular solid mass with malignant characteristics in the anterior mediastinum. Histopathological examination showed the picture and cytological effects of a primary mediastinal large B cell non-Hodgkin lymphoma, DD: Mediastinal seminoma. Immunohistochemical examination showed non-Hodgkin and diffused large B-cell lymphoma (DLBCL). The treatment was conducted with acetylcholinesterase inhibitors and pyridostigmine. The response to therapy with pyridostigmine was adequate, and complaints of MG symptoms such as dysphonia and dysphagia improved. After 10 treatments and radiotherapy, complaints of shortness of breath and other symptoms gradually eased.

Mediastinal tumors are primarily found in the anterior compartment and are more likely to be malignant, consisting of thymoma, lymphoma, and germ cell tumors [5]. This statement was consistent with the case series of mediastinal tumors where the first was with thymoma and the second was with a malignant tumor and lymphoma mediastinal. The clinical features of mediastinal tumors are related to compression or invasion of adjacent structures, leading to severe life-threatening emergencies. These tumors may be characterized by non-localized symptoms caused by paraneoplastic neurologic disease (PND). PND is not associated with tumor tissue invasion, distant metastases, or metabolic side effects/toxic effects of cancer therapy. Contrarily, it is triggered by an autoimmunity response to antigens that are co-expressed with tumors and target organs, such as the nerve and muscle tissue [6].

PND is a syndrome resulting from an abnormal immune response attacking the central and peripheral nervous systems associated with cancer [5–8]. Paraneoplastic syndrome occurs due to the secretion of functional peptides and hormones by tumors, cytokines, or immune cross-reactivity between malignant and normal tissue. The incidence was 8% in cancer patients and could affect the entire nervous system. PND occurred in various types of malignancy but was most commonly associated with small cell lung cancer (SCLC), ovarian cancer, breast cancer, neuroendocrine cancer, thymoma, and lymphoma [8].

In the first case, an anterior mediastinal tumor was thymoma with MG. This PND affected the peripheral nervous system, namely the neuromuscular junction, by antibodies against postsynaptic acetylcholine receptors (Anti-AChR). The PND was MG, while the tumor type was thymoma. Most MGs were not PND, but about 10–15% were cases with thymoma [7].

In the second case, an anterior mediastinal tumor was non-Hodgkin's lymphoma disease with MG. This case is associated with a paraneoplastic neurologic syndrome because treatment and management of cancer therapy with radiotherapy showed significant improvements in non-classical symptoms. The possibility suggested PND was

with the mechanism of the occurrence of an autoimmune process regarding the peripheral nerves in the neuromuscular junction. However, the possibility of PND required evidence of antibodies to cancer antigens against normal nerve cells, such as antibodies against receptors postsynaptic acetylcholine in syndromes associated with cancer such as anti-acetylcholine receptor (MG with thymoma), anti-VGCC (LEMS and PCD with small cell lung cancer), and anti-VGKC (limbic encephalitis) [12].

The pathogenesis of the paraneoplastic neurologic syndrome is not fully understood but is believed to be an immune system-mediated disorder. The paraneoplastic neurologic syndrome was rarely associated with Hodgkin's lymphoma (HL) and non-HL (NHL). The relationship between MG and thymoma had been identified, unlike that of MG and other malignancies. The relationship of MG to lymphoma with both mediastinal HL and mediastinal NHL was rarely associated, but there were case reports linked with paraneoplastic neurologic syndrome [12].

PND is associated with lymphoma and other paraneoplastic cerebellar degeneration (PCD) types. PCD is one of the PND, most commonly found in SCLC, breast tumors, ovarian tumors, and Hodgkin lymphoma. The syndrome manifests with prodromal symptoms such as dizziness, nausea, and vomiting that mimic peripheral vestibular symptoms, followed by ataxia, diplopia, dysarthria, and dysphagia [13]. Meanwhile, Tr antibodies are markers in PCD patients with Hodgkin lymphoma [13].

5 Conclusion

Myasthenia Gravis (MG) is an autoimmune disease caused by antibodies directed against acetylcholine receptors at the postsynaptic membrane, with the classic appearance of fluctuating weakness of the extraocular, bulbar, and proximal musculoskeletal muscles. Treatment of MG consists of symptomatic therapy, acetylcholinesterase inhibitors, immunosuppressant with steroids and non-steroids. Thymectomy could be a promising therapy option 1–2 years after diagnosis of early onset MG.

Mediastinal tumors are mostly and often found in the anterior compartment, consisting of thymoma, lymphoma, and germ cell tumors. The clinical manifestation may be related to compression or invasion of adjacent structures. These tumors can be characterized by non-local symptoms caused by paraneoplastic neurologic disease. The treatment in the first and second cases resulted in a clinically significant improvement in response to MG symptoms. Therefore, the two cases were closely related to paraneoplastic neurologic syndrome.

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