Myasthenic Crisis Caused By Preoperative Chemotherapy With Steroid for Advanced Thymoma

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We report the case of a 44-year-old woman with Masaoka stage IV, World Health Organization type B1 thymoma associated with pure red cell aplasia (PRCA), thrombocytopenia, and myasthenia gravis (MG), which occurred during preoperative chemotherapy with high-dose methylprednisolone. Noninvasive positive-pressure ventilation, intravenous immunoglobulin infusion, and methylprednisolone pulse therapy were performed for the myasthenic crisis. Disseminated thymoma was markedly reduced after these treatments, and macroscopic complete resection was performed after achieving control of PRCA, MG, and thrombocytopenia using cyclosporine A. Chemotherapy, including high-dose methylprednisolone, may carry a risk of MG, although the regimen is effective against lymphocyte-rich thymoma.


In patients with advanced thymoma, preoperative chemotherapy is occasionally indicated to achieve complete resection. However, the risk of the onset of MG (MG) during chemotherapy in patients with thymoma has received little attention. Here, we report a case of advanced thymoma associated with pure red cell aplasia (PRCA) and amegakaryocytic thrombocytopenia treated with preoperative chemotherapy that caused an acute-onset myasthenic crisis.

A 44-year-old woman presented complaining of shortness of breath and nonproductive cough. She had severe anemia (hemoglobin, 4.8 g/dL) with decreased reticulocytes (0.2%). Chest computed tomography revealed an anterior mediastinal mass 4.3 cm in diameter with suspected invasion to the pericardia and left brachiocephalic vein, multiple disseminations to the mediastinal pleura and diaphragm, and pleural effusion (Figs 1A, 1B). Pathologic diagnosis of World Health Organization type B1 thymoma was obtained from thoracoscopic biopsy specimen (Fig 1C). As a result, the patient was clinically diagnosed with Masaoka stage IVa, World Health Organization type B1 thymoma with PRCA. The patient’s antiacetylcholine receptor antibody level was elevated at 13 nmol/L (normal, <0.2 nmol/L), but no symptoms of MG were apparent at that time.

Because complete resection could not be expected, eight courses of chemotherapy using cisplatin (30 mg/m², day 1), vincristine (1 mg/m², day 1), doxorubicin (40 mg/m², day 1), and etoposide (80 mg/m², days 1 to 3) of a 7-day cycle were administered. Chest computed tomography showed disappearance of pleural effusion without tumor shrinkage, and the response was regarded as stable disease. As a second-line treatment, CAMP chemotherapy with cisplatin (20 mg/m², days 1 to 4), doxorubicin (40 mg/m², day 1), and methylprednisolone (1,000 mg/body weight, days 1 to 4 and 500 mg/body weight, days 5 to 6) was initiated.

On day 3, the patient experienced respiratory crisis of MG, diagnosed using the edrophonium test. Respiratory management was performed with noninvasive positive-pressure ventilation for 2 days, administration of intravenous immunoglobulin, and two courses of methylprednisolone pulse therapy, followed by oral administration of prednisolone (40 mg) every second day, resulting in improvement of the myasthenic crisis.

Fig 1. Chest computed tomography at diagnosis shows (A) an anterior mediastinal mass with suspected invasion to the pericardia and (B) a huge disseminated lesion on the diaphragm with pleural effusion. (C) Microscopic examination of the biopsy specimen shows small lymphocytes and atypical epithelia with clear cytoplasm, diagnosed as World Health Organization type B1 thymoma (hematoxylin and eosin staining, original magnification ×40).
Plasmapheresis was not necessary because the crisis was resolved immediately after intravenous immunoglobulin was administered.

Thrombocytopenia (platelet count, $2.0\times10^4/\mu L$) was observed 50 days after administration of CAMP therapy, whereas the white blood cell count remained within the normal reference range. A bone marrow biopsy specimen showed hypocellularity with marked decreases in megakaryocytes and reticulocytes. The reticulated platelet ratio was within the normal reference range, and serum thrombopoietin level was elevated to $1,050\,\text{pg/mL}$ (normal, $<106\,\text{pg/mL}$).

Cyclosporine A was administered for the management of thrombocytopenia and PRCA under a diagnosis of thymomatous autoimmune disorder, and the platelet count normalized within 20 days. Chest computed tomography showed marked shrinkage of the primary tumor and the disseminations (Figs 2A, 2B).

At 7 months after diagnosis, radical resection was performed through a right hemiclavshell incision. The preoperative antiacetylcholine receptor antibody level was at $13\,\text{nmol/L}$. In addition to extended thymectomy with thymoma resection, part of the right upper and middle lobes, the right phrenic nerve, pericardia, and left brachiocephalic vein were simultaneously resected because of direct invasion. Macroscopic complete resection, including disseminated lesions, was achieved, and diaphragmatic plication was added to prevent paradoxical diaphragmatic movement. The operative time was 478 minutes, and total blood loss was 1,450 mL.

Pyridostigmine was postoperatively administered for general fatigue and diplopia, which were considered to represent myasthenic symptoms, while the MG had been well controlled without a severe crisis. The patient was discharged home on postoperative day 20 in a stable condition.

Histopathologic examination showed lymphocytes and atypical epithelia spreading across organized tissue, probably influenced by the preoperative chemotherapy (Fig 2C). The patient underwent a repeat resection of relapsed left pleural dissemination 1 year later. PRCA, thrombocytopenia, and MG have since been adequately controlled, without symptoms, by oral administration of cyclosporine A (200 mg/d), prednisolone (15 mg every second day), and pyridostigmine (60 mg/d).

Comment

For advanced thymoma, multimodal therapy, including chemotherapy, has recently been performed in practice [1]. In addition to chemotherapy, steroids have been another option for the treatment of thymoma. In the thymoma tissue, nonneoplastic propagative T cells are mixed in varying proportions. Of those, $\text{CD4}^+\text{CD8}^+$ immature T cells display great susceptibility to glucocorticoids. Kobayashi and colleagues [2] reported that the overall response rate to steroid pulse therapy was 47.1% and that efficacy was most prominent in type B1 thymoma with abundant immature T cells. Likewise, Funakoshi and colleagues [3] reported that neoplastic epithelial cells in thymoma express glucocorticoid receptors, and glucocorticoids may directly affect tumor cells in addition to effects on associated lymphocytes. CAMP therapy, which includes high-dose methylprednisolone, was thus selected as the second-line approach for this patient.

Despite the absence of randomized studies, the efficacy of steroid therapy for MG is well recognized; however, steroid pulse therapy also carries a risk of transient exacerbation of myasthenic symptoms [4]. Because a myasthenic crisis actually developed in this patient just after CAMP therapy was initiated, high-dose methylprednisolone administration appears to warrant careful consideration not only in thymoma patients with MG but also in those with potential MG without symptoms. However, preoperative chemotherapy remains valuable against advanced thymoma, with complete surgical resection representing a well-known independent predictor of better prognosis [5].

A proportion of thymoma patients have clinically associated parathymomatous disorders, often characterized by an underlying autoimmune mechanism, with MG as the most common [6]. Others, including PRCA, hypogammaglobulinemia, and systemic lupus erythematosus, occur in approximately 5% to 10% of thymoma patients. Thrombocytopenia is rare, although described in some case reports. The treatment strategy could be complicated...
in patients with multiple parathymomatous associations, as in the present patient. Christensen and colleagues [7] suggested that the lower remission rate in MG patients showing associations with other autoimmune diseases might indicate a complex autoimmune response in patients with multiple autoimmune disorders. The successful treatment of PRCA and amegakaryocytic thrombocytopenia with cyclosporine A could suggest an autoimmunologic mechanism caused by thymoma. Immunosuppressive therapy may be a key management step to facilitate radical treatment of advanced thymoma.

In conclusion, we encountered a patient with thymoma associated with PRCA, amegakaryocytic thrombocytopenia, and MG triggered by preoperative chemotherapy. Although methylprednisolone may effective against type B1 thymoma, physicians must pay attention to the onset of a myasthenic crisis, even in patients with only potential MG.

References