Case report

In January 2008, a 31-year-old primigravid Chinese woman presented to the Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong, at 33 weeks’ gestation with shortness of breath, generalised limb weakness, drooping of the eyelids, and frequent choking. She had mild symptoms during the first and second trimesters, but did not seek medical attention or inform her obstetrician. Clinical examination revealed a gravid woman with bilateral ptosis, prominent fatigability, bilateral upper limb weakness, dysphonia, and tachypnoea. The forced vital capacity (FVC) was 1.09 L (22 mL/kg, 41% predicted value of FVC). Tensilon test showed rapid and marked symptom improvement. Myasthenia crisis was diagnosed in view of her respiratory and bulbar dysfunction.

The patient was transferred to the intensive care unit (ICU) where she received her first cycle of intravenous immunoglobulin (IVIG) at 0.4 g/kg/day for 5 days and started pyridostigmine at 60 mg 4 times a day via a nasogastric tube. The obstetrician recommended a course of intravenous dexamethasone 6 mg every 12 hours for 4 doses to treat possible intrauterine growth retardation. She improved slightly and was later transferred to the medical neurology ward for further care. Her condition deteriorated a few days later however, and she was readmitted to the ICU for close observation of respiratory and bulbar dysfunction. Bilevel positive airway pressure (BIPAP) was initiated. Oral prednisolone was started at 20 mg daily and pyridostigmine doses were gradually increased to 60 mg 7 times a day. At 35 weeks’ gestation, an elective caesarean section was performed. No neonatal myasthenia syndrome was noted in the infant.

There was no postpartum improvement in respiratory and bulbar symptoms and she remained dependent on ventilatory support. She developed fever with worsening respiratory effort and required intubation and ICU support a few days later. Blood culture showed coagulase-negative Staphylococcus species, which was likely to be due to intravenous catheter contamination, and azathioprine was stopped. She was given a second course of IVIG, but with little clinical response. She was noted to have persistent tachycardia and spiral computed tomography of the thorax showed features of pulmonary embolism and a possible ectopic thymoma at the anterior mediastinum.

The use of cyclophosphamide and rituximab for patients with refractory myasthenia gravis has shown promising results. We report on a 31-year-old Chinese woman with acetylcholine receptor antibody-negative and muscle-specific tyrosine kinase antibody–positive generalised myasthenia gravis who had refractory bulbar dysfunction and respiratory failure despite immunosuppressive therapy and thymectomy, and partial and sustained responses to cyclophosphamide and rituximab treatment, respectively. Myasthenia crisis was diagnosed when she presented in the third trimester of pregnancy with dysphagia, bilateral ptosis, prominent fatigability, and respiratory failure. She required prolonged intensive care and non-invasive ventilatory support despite several courses of intravenous immunoglobulins and plasmapheresis. Pulse cyclophosphamide 500 mg/m² was given monthly for 4 consecutive months with a partial response. Rituximab 500 mg weekly was subsequently given for 4 weeks with a dramatic and sustained response. She remained symptom-free and assumed full maternal care at 1 year. To the authors’ knowledge, this is the first report of a Chinese patient with refractory myasthenia gravis who responded to cyclophosphamide and rituximab.

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There was no postpartum improvement in respiratory and bulbar symptoms and she remained dependent on ventilatory support. She underwent a course of plasmapheresis, consisting of six exchanges. Pyridostigmine was increased to 450 mg per day, and she started azathioprine at 50 mg daily orally. She improved slightly and was discharged to the general ward.

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muscle-specific receptor tyrosine kinase (MuSK) antibody. In view of the refractory myasthenia gravis, pulse cyclophosphamide 500 mg/m² was initiated. Cyclophosphamide was given at 500 mg, 750 mg, 1000 mg, and 1000 mg for 4 consecutive months. There was transient improvement for 1 to 2 weeks after each course of pulse cyclophosphamide, but her condition deteriorated again 3 to 4 weeks after each course, and she required BIPAP support. She was then given rituximab infusion at 500 mg weekly for 4 consecutive weeks, and showed dramatic improvement with her FVC reaching 1.5 L (33 mL/kg, 56% predicted), and she was discharged 8 months after admission (Fig). She continued to improve at home and began to care for her 7-month-old boy.

Serological test results were negative for acetylcholine receptor (AChR) and positive for muscle-specific receptor tyrosine kinase (MuSK) antibody. In view of the refractory myasthenia gravis, pulse cyclophosphamide 500 mg/m² was initiated. Cyclophosphamide was given at 500 mg, 750 mg, 1000 mg, and 1000 mg for 4 consecutive months. There was transient improvement for 1 to 2 weeks after each course of pulse cyclophosphamide, but her condition deteriorated again 3 to 4 weeks after each course, and she required BIPAP support. She was then given rituximab infusion at 500 mg weekly for 4 consecutive weeks, and showed dramatic improvement with her FVC reaching 1.5 L (33 mL/kg, 56% predicted), and she was discharged 8 months after admission (Fig). She continued to improve at home and began to care for her 7-month-old boy.

Discussion

Myasthenia gravis is a well-characterised autoimmune disorder of the skeletal muscle caused by reduced AChRs at the neuromuscular junction. Acetylcholine receptor antibodies are found in 80 to 90% of patients...
with myasthenia gravis. In 50% of the remaining ‘seronegative’ patients, antibodies to MuSK surface membrane enzymes are present. These patients are usually women, with predominant facial and bulbar involvement, and a high rate of respiratory crisis, despite variable or minimal limb weakness. Importantly, these patients usually have only a partial response to steroid and pyridostigmine therapies and present management challenges to clinicians.

Cyclophosphamide treatment was given to this patient because of the published success in patients matching the clinical profile of this patient. The use of high-dose cyclophosphamide has been shown to cause symptom improvement and sustained control. This medication is readily available at the Prince of Wales Hospital and was offered to this patient when her condition remained refractory after 4 months of treatment. Dose titration by approximately 25% each month was suggested in the published studies. Unfortunately, she failed to show a sustained response to cyclophosphamide.

Rituximab is a chimeric human-mouse CD-20 monoclonal antibody that depletes CD-20–positive B-cells and has demonstrated efficacy against various haematological and rheumatological disorders, such as lymphoma and rheumatoid arthritis. The first report of the use of rituximab in patients with myasthenia gravis was in 2004, in which the patient had co-existing B-cell non-Hodgkin lymphoma—the original indication for rituximab. Since then several case reports or series have reported an excellent response, including complete remission, for patients with refractory myasthenia gravis treated with rituximab. All of the published patients had good tolerance and clinical response to rituximab. This patients’ family understood the off-label use and decided to proceed with treatment despite the relatively high cost. The major side-effects, which are mostly associated with infusion of the medication, were not observed in this patient.

The sustained response of this patient is likely to be due to the cumulative effect of post-thymectomy and immunosuppressive treatment with azathioprine and prednisolone, rather than to rituximab alone. Due to the high cost of rituximab treatment, it was agreed with the patient and family to reserve it for use for relapse and crisis rather than for prophylaxis or maintenance. Nonetheless, some case series have suggested the usefulness of maintenance treatment with rituximab. Published reports of rituximab are sparse and consist mainly of case reports and short case series. The results from the first phase II randomised control trial on the use of rituximab in this group of patients are eagerly awaited, as a recent review of the treatment for myasthenia gravis highlighted the lack of evidence-based studies of treatment options for patients with myasthenia gravis, despite reduced mortality rates and improved quality of life with treatment. Steroids remain the first-line immunosuppressive treatment, followed by azathioprine, cyclosporine, and mycophenolate. Intravenous immunoglobulins or plasma exchange are useful for myasthenia crisis, and rituximab or cyclophosphamide could be considered for patients with severely drug-resistant disease.

**Conclusion**

The use of rituximab for refractory anti-AChR-negative, MuSK-positive myasthenia gravis appears to be a promising treatment option. Nonetheless, more clinical data, especially from randomised controlled trials, are needed.

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**References**