Myasthenia gravis and a rare complication of chemotherapy

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We describe a patient with myasthenia gravis and thymoma who developed recurrent severe myasthenic crises associated with the use of combination chemotherapy. **(MJA 2005; 182: 120)**

Myasthenia gravis (MG) is an uncommon immunological disorder of the neuromuscular junction that is characterised by abnormal weakness and fatigability of some or all striated voluntary muscles. It is the most common autoimmune disorder in patients with thymoma, in whom the incidence is 30%–50%.[1]

In patients with MG, up to 90% of their acetylcholine receptors may be destroyed by autoantibodies, predisposing them to disease exacerbation by any agent that impedes neuromuscular transmission.[2]

Clinical record

In February, a 49-year-old self-employed builder developed MG and was subsequently found to have invasive thymoma. This was incompletely excised. The surgical procedure was complicated by left phrenic nerve palsy.

In May, the patient commenced his first cycle of chemotherapy, which was to comprise doxorubicin 50 mg/m^2 Day 1, cisplatin 100 mg/m^2 Day 1 and etoposide 120 mg/m^2 Days 1, 3 and 5, with dexamethasone 20 mg, ondansetron 8 mg and metoclopramide 10 mg administered before chemotherapy to control nausea. His MG had been well controlled on pyridostigmine 60 mg twice daily. However, within 24 hours of the first dose of chemotherapy, he developed a severe myasthenic crisis with respiratory failure requiring intubation. This was managed with dexamethasone 8 mg daily and plasmapheresis, and was thought to be due to the high-dose dexamethasone given prior to chemotherapy. In addition, he had developed a chest infection a couple of days before starting chemotherapy, which may have contributed to the respiratory failure. A methicillin-sensitive *Staphyloccus aureus* was isolated from sputum cultures. This was managed upon hospitalisation with intravenous ceftriaxone 1 g daily for 7 days.

In June, the patient received his second cycle of chemotherapy, this time without dexamethasone. Within several hours, he developed increasing breathlessness with bulbar dysfunction and generalised weakness. Despite treatment with steroids and intravenous neostigmine, his respiratory state continued to deteriorate, necessitating intubation and subsequent plasmapheresis.

No further cycles of chemotherapy were administered. A restaging computed tomography scan at the time revealed minimal residual tumour and mediastinal lymphadenopathy. In August, he completed a course of mediastinal radiotherapy that was complicated by mild radiation pneumonitis.

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Discussion

A review of the literature revealed no previous report of MG unmasked or aggravated by chemotherapeutic agents. However, several other classes of drugs have been associated with exacerbation of pre-existing MG. Aminoglycosides have been most frequently associated with drug-induced neuromuscular blockade. However, agents most likely to cause aggravation of MG when overused are anticholinesterase drugs, high-dose prednisolone, anaesthetic agents and neuromuscular blockers. Immunosuppressive drugs have also been implicated,[3] and transient worsening of MG by high-dose corticosteroids is commonly encountered.[4] Miller and colleagues[5] found a positive correlation between serum methylprednisolone sodium succinate concentrations and deterioration in neuromuscular transmission. No effect on acetylcholine-receptor antibodies was noted. They speculated that the effects of steroids on MG arise from dissociation of nerve excitation and muscle contraction.

Our patient developed recurrent severe myasthenic crises despite the omission of steroids in his second cycle of chemotherapy. It is highly likely that at least one of the three chemotherapeutic agents used had a direct inhibitory effect on neuromuscular transmission, aggravating pre-existing MG. The adverse drug reaction was assessed as "probable" based on a score of 5 on the Naranjo Adverse Drug Reaction Probability Scale.[6] The exact mechanism for the neuromuscular blockade is uncertain, but may be due to disrupted calcium entry into the presynaptic nerve terminal, inhibiting presynaptic acetylcholine release. Alternatively, it may be due to postsynaptic blockade, the drugs may bind competitively to the acetylcholine, or may interfere with ionic conductance across the muscle membrane.[7] A combination of pre- and post-synaptic blockade may also occur.

Competing interests

None identified.

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