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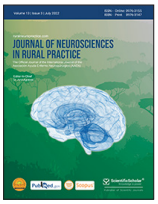

Case Report

Myocarditis-myositis-myasthenia gravis overlap syndrome depending on immune checkpoint inhibitor

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ABSTRACT

Immune checkpoint inhibitors are breakthrough monoclonal antibodies in cancer therapy developed against mechanisms that suppress the immune response. After the devastating effects of chemotherapy, these specific agents have given hope to cancer patients. However, every drug has side effects itself and these useful drugs have theirs too. In addition to systemic side effects, there are also neurological side effects, the frequency of which is increasing day by day, although they are reported very rarely for now. Here, we present a case that has myositis-myocarditis-myasthenia gravis overlap syndrome. These three syndromes are very rare even to be seen alone, which are detected together. This syndrome with a very high mortality was brought under control in this case, and the fact that nivolumab treatment can be continued makes the case even more interesting. In this article, it is aimed to draw attention to this serious triple complication of immune checkpoint inhibitors and to review the relevant literature on a case basis.

Keywords: Myasthenia gravis, Myositis, Myocarditis, Immune checkpoint inhibitor

INTRODUCTION

Immune checkpoint inhibitors (ICIs), which were first approved by the FDA in 2011, act by inhibiting molecules that provide lymphocyte apoptosis.[1,2] ICIs have many immunological side effects depending on increased immune response and autoimmunity. These side effects may affect many organs and systems and can be mild (Stages 1–2), severe (Stages 3–4), or life threatening (Stage 5).[3] In addition to systemic side effects, there are also neurological side effects, the frequency of which is increasing day by day, although they are reported very rarely for now.[3,4]

Our case is a myositis-myocarditis-myasthenia gravis overlap syndrome, which is very rare even to be seen alone, is detected together. In this article, it is aimed to draw attention to this serious triple complication of ICIs and to review the relevant literature on a case-by-case basis.

CASE REPORT

A 33-year-old male patient was admitted to the neurology clinic with the complaints of double vision, difficulty in speaking, and paresthesia in the hands and feet. The patient had a history of thymoma (pleural metastasis, stage 4) diagnosed 1 year ago was undergone thymectomy operation. He had been receiving combination chemotherapy for 1 year. Nivolumab (240 mg), an ICI, was started due to progression in the patient. Complaints started after 3 months of nivolumab therapy. There was inward gaze limitation in the right eye, binocular diplopia, and hypernasal speech but no ptosis. Muscle strength examination was normal. There was hypoesthesia in the distal lower and upper extremities bilaterally.

Cranial MRI was normal. Electroneuromyography studies performed in the polyneuropathy and myasthenia protocol were within normal limits. Anti-acetylcholine receptor antibody was found negative. Oral pyridostigmine was started but no response was obtained. The patient, who was evaluated as myasthenic crisis, was administered IVIG treatment at 0.4 g/kg/day for 5 days. Partial control of bulbar symptoms was achieved.

Three weeks later, the patient was re-evaluated. He had diplopia and hypernasal speech, 500 mg IV pulse steroid therapy was administered for 5 days and maintained with oral prednisolone 15 mg/day. Significant improvement was observed in all neurological complaints of the patient. Maintenance oral steroid therapy was gradually increased to 30 mg/day.

Nivolumab treatment was recommended to be discontinued. Because of the cure was achieved with this treatment; it was continued under close follow-up after obtaining informed

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consent by the oncology department. In the muscle biopsy of the patient who developed weakness and muscle pain and had serum CK: 426 U/L (0–190), histopathological findings, which were evaluated in favor of myositis, were observed. The patient was also diagnosed with myocarditis as a result of consultation for possible cardiac involvement. It was planned to discontinue the oral steroid gradually of the patient who was being followed up with oral prednisolone 30 mg/day, due to exanthematous skin lesions, those were associated with steroid-induced acne. Azathioprine 25 mg 2 × 1 was started as a disease-controlling agent for myasthenia gravis.

There was a partial increase in the patient's neurological complaints in the control visit. IVIG treatment at 0.4 g/kg/day was administered to patient for 5 more days. Neurological symptom control was achieved after this treatment. The azathioprine taken by the patient was increased to 100 mg/day. The patient, whose symptom control was achieved with the current treatment, still continues to receive nivolumab treatment under close follow-up.

DISCUSSION

ICIs have many immunological side effects depending on increased immune response and autoimmunity.[1,2] Although neurological involvement seems to constitute a very small part (<1%) of these side effects, the number of cases increases as the treatments continue.[3,4] ICIs may show their neurological side effects on the central nervous system, peripheral nervous system, neuromuscular junction, and muscles. Neurological side effects can be classified as non-specific side effects defined as stages 1–2, stages 3–4 serious side effects, and life-threatening side effects.[1-5] ICIs can be continued with supportive treatment in Stage 1, but it is necessary to discontinue the ICI applied from Stage 2 onward. Oral or intravenous steroids are preferred in the first step of treatment. Prednisolone dose adjustment should be carried out according to the severity of the symptoms (0.5–2 mg/kg/day). If no adequate response could be achieved with steroid, intravenous immunoglobulin or plasmapheresis options should be considered. Steroids can be combined with IVIG/plasmapheresis. If no response is obtained with all these, additional immunosuppressive agents can be used. Cyclophosphamide, rituximab, and anti-TNF-alpha antibodies are other treatment options. There is insufficient evidence regarding the efficacy of azathioprine and mycophenolate mofetil.[1-4] Furthermore, in our case, IVIG, steroid was used for maintenance and azathioprine was used for symptom control. The patient is still being followed up with azathioprine.

Myocarditis-myositis-myasthenia gravis overlap syndrome, in which peripheral nervous system-muscle-neuromuscular junction diseases coexist, which was also seen in our patient, is an extremely rare and dangerous complication of ICIs. A total of 60 patients were reported in the literature, and only one of them had a previously known autoimmune disease.[4,5]

While the most common complaints were fatigue and muscle weakness, 60% of the patients were dead.[4] Our case is very rare in terms of both being observed after thymoma and developing symptoms 12 weeks after nivolumab treatment. In addition, this syndrome with a very high mortality was brought under control in this case, and the fact that nivolumab treatment can be continued makes the case even more interesting.

CONCLUSION

Myocarditis-myositis-Myasthenia gravis overlap syndrome, in which peripheral nervous system-muscle-neuromuscular junction diseases coexist, is an extremely rare and dangerous complication of immune checkpoint inhibitors. This life-threatining complication often requires to cut the treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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None.

Conflicts of interest

There are no conflicts of interest.

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