ESETISMERTETÉS

CASE REPORT

Pembrolizumab-induced peripheral nervous system damage: A combination of myositis/ myasthenia overlap syndrome and motor axonal polyneuropathy

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Introduction – Immune-checkpoint inhibitors (ICI) are effective drugs in cancer treatment that block immune checkpoints and stimulate an attack on cancer cells. However, various side effects were reported with ICIs. Peripheral nervous system (PNS) side effects are three times more frequent than those in the central nervous system.
Case report – A 63-year-old male patient was admitted to our department with a 10-day history of dyspnea, diplopia, and generalized weakness. He had a diagnosis of non-small cell lung cancer, which was treated with pembrolizumab. His neurological symptoms appeared one week after the second course of pembrolizumab, and gradually worsened. His neurological examination showed nasal speech, bilateral ptosis, tongue and neck flexor weakness, prominent asymmetrical upper limb weakness, and mild lower limb weakness. Deep tendon reflexes and sensory examination were normal. He had an elevated creatine kinase level (4430 U/L). Needle electromyography (EMG) showed a myopathic pattern, and single fiber EMG demonstrated an increased jitter in the right frontal muscle. Pembrolizumab treatment was discontinued, and intravenous methylprednisolone followed by intravenous immunoglobulin (IVIg) were initiated. His symptoms gradually improved. However, his weakness began to worsen after a month, and repeated nerve conduction studies

Pembrolizumab által kiváltott perifériás idegrendszeri károsodás: A myositis / myasthenia overlap szindróma és a motoros axonalis polyneuropathia kombinációja

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Bevezetés – Az immunellenőrző pontokat blokkoló immunellenőrzőpont-gátlók (ICI-k) hatékony gyógyszerek a rák kezelésében, mivel segítik a rákos sejtek elleni támadás beindulását. Mindazonáltal, az ICI-kkel kapcsolatban számos különböző mellékhatásról számoltak be. A perifériás idegrendszeri (PNS) mellékhatások háromszor gyakoribbak, mint a központi idegrendszeri mellékhatások.
Esetismertetés – Egy 63 éves férfi beteget 10 napja fennálló nehézlégzéssel, diplopiával és generalizált gyengeséggel vettek fel osztályunkra. Korábban nem kissejtes tüdőrákot diagnosztizáltak nála, amit pembrolizumabbal kezeltek. Neurológiai tünetei egy héttel a második pembrolizumabciklus után jelentek meg, és fokozatosan romlottak. Neurológiai vizsgálata orrhangú beszédet, kétoldali ptosist, a nyelv- és a nyakhajlító izmok gyengeségét, markáns aszimmetrikus felső végtagi gyengeséget és enyhe alsó végtagi gyengeséget mutatott. A mély ínreflexek és az érzékszervi vizsgálat normális volt. A kreatinkináz szintje emelkedett volt (4430 E/l). A tűelektromiográfia (EMG) myopathiás mintázatot mutatott, és az egyszálas EMG fokozott remegést mutatott a jobb frontális izomban. A pembrolizumabkezelést abbahagyták, és intravénás metilprednizolon, majd intravénás immunglobulin (IVIg) adását kezdeményezték. A beteg tünetei fokozatosan javultak. A gyengesége azonban egy hónap múlva súlyosbodni kezdett, és az ismételt idegvezetési vizs-

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showed a predominantly motor axonal polyneuropathy. Thereafter, the patient was treated with IVIg infusions (0.4 g/every two weeks) to maintain his motor function.
Conclusion – Our case showed that ICIs could simultaneously or sequentially cause damage in multiple domains of the PNS. Early recognition of these adverse events is essential since the outcome is favorable with rapid cessation of the causative ICI and administration of immune-modulator treatment.

Keywords: immune checkpoint inhibitor, polyneuropathy, myasthenia gravis, myocarditis, intravenous immunoglobulin

gálatok túlnyomórészt motoros axonalis polyneuropathiát mutattak ki. Ezt követően a beteget IVIg-infúziókkal (0,4 g/kétheten-te) kezelték a motoros funkció fenntartása érdekében.
Következtetés – Betegünk esete azt mutatja, hogy az ICI-k egyidejűleg vagy szekvenciálisan károsodást okozhatnak a PNS több területén. E mellékhatások korai felismerése alapvető fontosságú, mivel a kiváltó ICI-kezelés gyors abbahagyásával és immunmoduláns kezeléssel kedvező a kimenetel.

Kulcsszavak: immunellenőrzőpont-gátló, polyneuropathia, myasthenia gravis, myocarditis, intravénás immunglobulin

Immune-checkpoint inhibitors (ICI) recently emerged as a state-of-art therapy for numerous cancer types. By blocking immune checkpoints, which are down-regulators of the immune system to induce tolerance for self-cells, they stimulate an attack on cancer cells. Owing to their high efficacy, the number of ICIs is rapidly expanding. The primary target of the ICIs includes T-lymphocyte-associated antigen 4, programmed cell death protein-1, and its ligand[1]. Although they are highly effective in cancer treatment, various side effects, primarily related to over-activation of the immune system, were reported with ICIs. In a large meta-analysis, the most frequent immune-mediated adverse events included hypothyroidism, vitiligo, hepatitis, pneumonitis, colitis, and hypophysitis[2]. Overall, neurological side effects occur in 1% of the patients. Among them, peripheral nervous system (PNS) involvement, including myasthenic syndrome, myositis, Guillain-Barré syndrome and other peripheral neuropathies, is three times more frequent than central nervous system (CNS) involvement[3]. ICI-related myasthenic syndrome (IrMG) and myositis (IrMyositis) typically manifest with peculiar symptoms and occur separately or in combination, suggesting a distinct myositis/myasthenia overlap syndrome. On the other hand, co-occurence of myositis/myasthenia overlap syndrome, and ICI-related peripheral neuropathy (IrPN) was only reported in a single case report[4]. Here, we describe a patient with non-small cell lung cancer who had a sequential occurrence of myositis/myasthenia overlap syndrome and axonal polyneuropathy.

Case description

A 63-year-old male patient was admitted to our department with a 10-day history of fatigable dyspnea, diplopia, and generalized weakness. Five days before his admittance, he was diagnosed with myasthenia gravis and prescribed prednisolone 80 mg/day and pyridostigmine 60 mg, four times a day, but his symptoms continued worsening. His past medical history was significant for non-small cell lung cancer which was initially treated with cisplatin and pemetrexed. After two cycles, pembrolizumab was added. Although a therapeutic response was achieved with this treatment, one week after the second course of pembrolizumab his neurological symptoms appeared and gradually worsened. He was also using amiodarone 200 mg/day for inducible ventricular fibrillation. His family history was unremarkable.

His neurological examination showed nasal speech, asymmetrical bilateral ptosis, bilateral limitation of lateral gaze, tongue weakness, neck flexor weakness, asymmetrical proximal and distal weakness in the upper, and symmetrical weakness in proximal lower limb muscles. Deep tendon reflexes and sensory examination were normal. Blood biochemistry analysis revealed elevated creatine kinase (4430 U/L) and troponin T (942 pg/mL) levels. Needle EMG showed myogenic motor unit potentials in all examined muscles **(Figure 1A)** accompanied by positive sharp waves. Repetitive nerve stimulation test from the right trapezius muscle was normal. However, an increased jitter was observed in the right frontal muscle

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(Figure 1B). Nerve conduction studies were normal **(Figure 2A, 2B)**. Acetylcholine receptor antibodies (Anti-AchR), muscle-specific kinase antibodies (Anti-MuSK), and the paraneoplastic antibody panel were negative (Anti-Hu, anti-Yo, Anti-Ri, Anti-amfifizin, Anti-NMDAR, Anti-VGKC). Anti-titin antibodies were positive in the myositis-associated antibody panel. Pulmonary function tests and arterial blood gas analysis revealed a restrictive ventilatory impairment, and non-invasive mechanical ventilation was initiated.

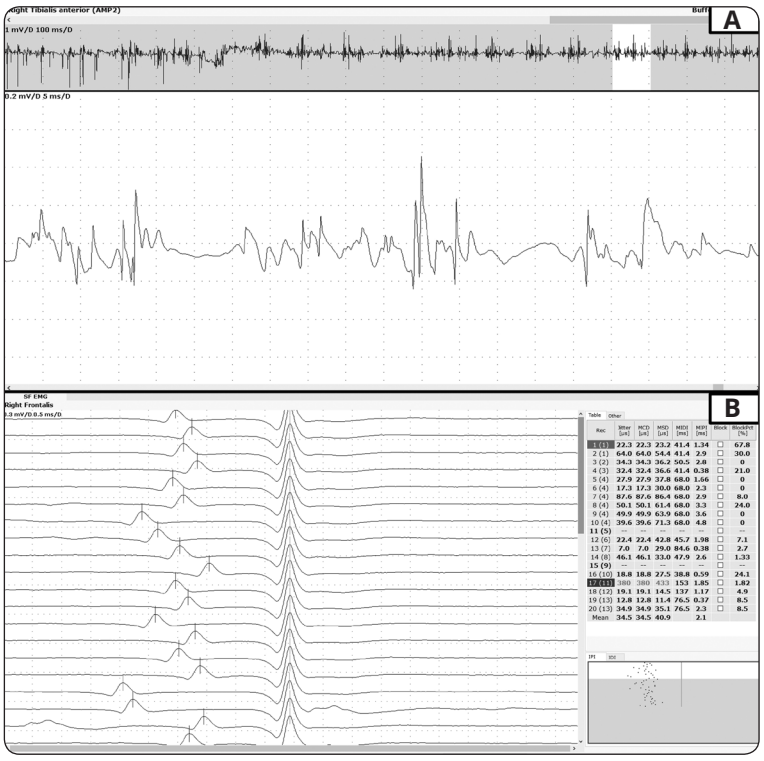

Figure 1. *Needle electromyography* **(1A)** *of the right tibialis anterior muscle demonstrated myogenic motor unit potentials and single fiber electromyography* **(1B)** *showed an increased jitter in the right frontal muscle*

With these findings, a diagnosis of myositis/myasthenia overlap syndrome was made and pembrolizumab treatment was immediately discontinued. Intravenous methylprednisolone 1000 mg/day for five days followed by intravenous immunoglobulin (IVIg) 2 g/kg were initiated and pyridostigmine was stopped due to a lack of meaningful clinical response. After one week, his symptoms gradually improved with only a residual mild weakness bilaterally in finger extensors, and iliopsoas. Electrocardiograph, echocardiography, and cardiac MRI were negative for accompanying myocarditis. He was discharged from the hospital with oral prednisolone 60 mg/day and monthly infusions of IVIg 0,4 g/kg. However, after a month, his weakness began to worsen, predominantly in the upper extremities. In addition to muscle weakness, deep tendon reflexes were absent, except for bilateral hypoactive triceps reflex and he had hypoesthesia and hypoalgesia in the distal parts of the lower limbs. Therefore, nerve conduction studies were repeated which showed a predominantly motor axonal polyneuropathy **(Figure 2C, 2D)**. CK level was normal (61 U/L), and troponin T level decreased to 180 pg/mL. A slightly elevated protein level (49 mg/dl) without pleocytosis was observed in cerebrospinal fluid (CSF) analysis. Hence, another course of IVIg 2 g/kg was initiated for the possibility of IrPN. Progression of weakness stopped with this treatment, and he was discharged with prednisolone 40 mg/day. Follow-up scans were compatible with remission in his underlying malignancy. Therefore, cisplatin and pemetrexed were also stopped. Three weeks after, his symptoms relapsed with increased weakness, more pronounced in the upper limbs. Repeated NCS showed a decrease in the motor amplitudes in the upper limb nerves. CK level was normal. Thus, a repeated dose of IVIg 0,4 g/kg was initiated. However, his symptoms continued to worsen in the following week, and another loading dose of IVIg (2 g/kg) was given. His symptoms stopped worsening with this treatment. However, the remission period lasted for two weeks, a repeated IVIg (1 g/kg) infusion was required. Thereafter, the patient was treated with IVIg infusions (0,4 g/every two weeks) to maintain his motor function and he was put on a steroid tapering scheme. According to Naranjo's adverse drug reaction assessment score of 6, IrMyositis, IrMG, combined with IrPN were probably caused by pembrolizumab.

Discussion

Here, we report a patient exhibiting a combination of myositis/myasthenia overlap syndrome, and polyneuropathy after pembrolizumab treatment. Although ICI-related neuromuscular system damage is rare, it can be life-threatening. The most frequent neuromuscular syndromes associated with ICIs are myositis, myasthenic syndrome, demyelinating polyradiculoneuropathy, and overlaps of these conditions[5]. Presentation and disease course of ICI-related neuromuscular conditions differ from the typical forms of these disorders.

Like in the case of our patient, IrMyositis typically occurs in the first three months of ICI treatment and progresses to a peak in 1-30 days[5]. Initially, our patient had proximal and distal weakness in the upper limbs accom-

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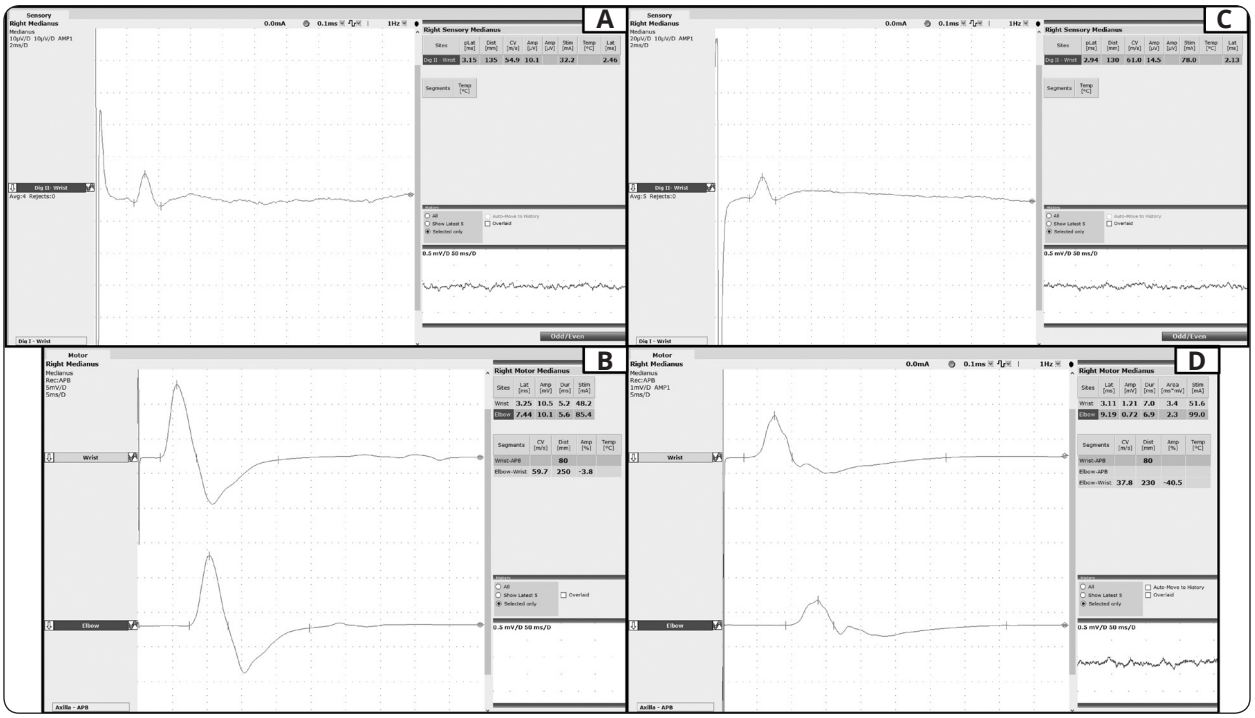

Figure 2. *In nerve conduction studies, median sensory nerve action potential (SNAP) and median motor compound motor action potential (CMAP) were normal in the initial test* **(2A and 2B)**. *On the other hand, median motor CMAP amplitude was markedly decreased in the repeated test, whereas median SNAP remained normal* **(2C and 2D)**

panied by proximal weakness in the lower limbs. Along with this, oculo-bulbar muscle involvement was prominent. Likewise, the typical presentation of the previously published cases includes axial and limb-girdle weakness accompanied by oculomotor and bulbar involvement. In addition, 20% of patients with IrMyositis need non-invasive or invasive ventilatory support like our patient[6]. The diagnosis of myositis was straightforward in our patient due to a subacute muscle weakness and hyperCKemia with typical EMG findings. Therefore, we did not perform a muscle biopsy.

Around 30% of IrMyositis overlap with IrMG, which can present with a severe disease course and have fatal outcome[5]. On the other hand, approximately 20% of the patients only exhibit mild ocular symptoms. The impact of the myasthenic component in IrMyositis is a matter of debate since ocular involvement can also be observed in IrMyositis. Meanwhile, like in the case of our patient, a clear benefit from cholinesterase inhibitors may not be evident in patients with a myositis/myasthenia overlap syndrome[7]. Anti-AChR antibodies can be observed in about half of the patients, whereas Anti-MuSK was found only in a single patient previously[8]. Both antibodies were absent in our patient. On the other hand, anti-titin antibody test was positive. Interestingly, it was previously reported in patients with a combination of idiopathic inflammatory myopathy and myasthenia gravis without ICI use[9, 10]. Although this suggests the possibility of a mechanistic role of anti-titin in the combination of these disorders, future studies are necessary to conclude its function in myositis/myasthenia overlap syndrome. The reported incidence of ICI-related myocarditis is up to 1.14%. It is more frequent with an accompanying IrMG or IrMyositis[6]. Although cardiac MRI was normal, highly elevated troponin-T could suggest at least a minor cardiac involvement in our patient.

IrPN occurs in 1-3% of patients in previous case series and tends to present after a median of 3-3.5 doses of ICIs, later than the typical onset of myositis/myasthenia overlap syndrome[11]. The most common presentation is acute or chronic inflammatory demyelinating neuropathy. Other reported neuropathy types were cranial, small fiber neuropathies, ANCA-associated mononeuritis multiplex, sensory neuronopathy, length-dependent sensorimotor axonal polyneuropathy, and neuralgic amyotrophy[12]. Our patient had an acute onset pure motor axonal neuropathy, mimicking an acute motor axonal neuropathy (AMAN). However, course of the neuropathy was progressive. Although it is difficult to attribute axonal changes only to ICIs, since our patient also underwent a cytotoxic chemotherapy in addition to pembrolizumab, the acute-onset with therapeutic response to IVIg and an albumino-cytologic dissociation suggested inflammatory mechanism. For the treatment of IrPN, the immediate discontinuation

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of ICIs is uncontroversial. Corticosteroids are not recommended for the treatment of AMAN or typical Guillain-Barré syndrome (GBS). On the other hand, in ICI-related GBS, steroids are considered as first-line treatment option in the guidelines of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)[13, 14]. We hesitated to use high-dose steroids in our patient because that could lead to a potential exacerbation which was described in the motor forms of chronic immune-mediated neuropathies such as multifocal motor neuropathy and motor chronic inflammatory demyelinating neuropathy[15]. Typically, the outcome is described to be favorable with steroids and discontinuation of ICIs in IrPN and maintenance therapy are usually not required[12]. However, our patient significantly deteriorated between IVIg doses, and showed an IVIg-dependent clinical course.

Conclusion

Although ICIs revolutionized cancer treatment, adverse events can be life-threatening. Our case showed that ICIs could simultaneously or sequentially cause damage in multiple domains of the peripheral nervous system. Early recognition of these adverse events is of the utmost importance since the outcome is favorable with rapid cessation of the causative ICI and administration of immune-modulator treatment.

DECLARATIONS – Informed consent to publish the case report was obtained from the patient.
CONFLICTS OF INTEREST AND SOURCE OF FUNDING – None declared.

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