



Chronic Inflammatory Demyelinating Polyneuropathy Induced by Immune Checkpoint Inhibitors: Case Reports

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Abstract

Neurological immune-related adverse events (irAE) are rare but potentially fatal complications associated with the use of immune checkpoint inhibitors (ICI). Recently, there has been a trend towards an increase in the incidence of these cases.

We present two case reports of demyelinating polyneuropathy in patients with skin melanoma treated with pembrolizumab or nivolumab. Unawareness of neurological irAE induced by ICI leads to delayed diagnosis and medical treatment, and this may result in persistent neurological deficit or even patients' death. Neurological irAEs include myasthenia gravis, aseptic meningitis, encephalitis, inflammatory demyelinating neuropathy, myositis or their combinations, etc. Considering their variability in patients treated with ICI and poor representation in publications, each case report can be of practical value.

Keywords: monoclonal antibodies; immune checkpoint inhibitors; pembrolizumab; nivolumab; neurological complications; dysimmune polyneuropathy; chronic inflammatory demyelinating polyneuropathy

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the I. Kant BFU (protocol No. 34, September 29, 2022).

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Хроническая воспалительная демиелинизирующая полинейропатия на фоне применения ингибиторов контрольных точек: клинические наблюдения

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Аннотация

Неврологические нежелательные явления (ННЯ), связанные с применением ингибиторов контрольных точек (ИКТ), являются редкими, но потенциально фатальными осложнениями. За последние годы отмечается тенденция к росту регистрации данных случаев. Мы приводим два клинических случая демиелинизирующей полинейропатии у пациентов с меланомой кожи на фоне лечения пембролизумабом и ниволумабом. Отсутствие осведомлённости о ННЯ при применении ИКТ ведёт к задержке постановки правильного диагноза,

вследствие этого – к отсроченному назначению лекарственной терапии и развитию стойкого неврологического дефицита, вплоть до летального исхода. Среди ННЯ выделяют миастению, асептический менингит, энцефалит, миелит, воспалительную демиелинизирующую нейропатию, миозит или их сочетания и др. С учётом их variability при использовании ИКТ и малой представленности в мировой литературе описание каждого клинического случая при применении данных лекарственных средств имеет практическую ценность.

Ключевые слова: моноклональные антитела; ингибиторы контрольных точек; пембролизумаб; ниволумаб; неврологические осложнения; дизимунная полинейропатия; хроническая воспалительная демиелинизирующая полинейропатия

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

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Introduction

Mechanisms underlying immune evasion of tumor cells include increased expression of immune checkpoints (ICs) and their ligands regulating signaling pathways that influence the magnitude and duration of immune response, as well as tolerance of immune cells to their own antigens. Besides conventional chemotherapy, advances in the development and implementation of immune therapies targeting ICs for cancer patients led to a new class of neurological complications, which often remain unrecognized by neurologists and oncologists. This type of monoclonal antibodies is used for the treatment of metastatic malignant tumors and melanoma by enhancing natural antitumor response [1, 2]. Experience with these agents is rapidly growing, and the most studied immune checkpoint inhibitors (ICIs) include agents that target cytotoxic T-lymphocyte associated protein 4 (CTLA-4), such as ipilimumab and tremelimumab; programmed cell death protein-1 (PD-1), such as nivolumab, pembrolizumab, cemiplimab, and dostarlimab; and its ligands (programmed cell death ligand PD-L1, PD-L2), such as atezolizumab and durvalumab. Monotherapy is more common, while combination therapy with anti-PD-1 and anti-CTLA-4 is

used less often [3]. Lymphocyte activation and restoration of antitumor immune response occur due to blocking of IC signaling pathways [1, 4]. However, PD-1/PD-L1 and CTLA-4 are widely expressed not only by cancer cells but also by other cell types; therefore, a wide range of autoimmune reactions can occur if they are suppressed. Neurological immune-related adverse events (irAEs) occurred approximately in 1–6% of patients treated with ICIs and affected both the peripheral and central nervous systems [5]. Most neurological irAEs were reported in 2017–2018 (61–78% of cases), reflecting the substantially increased use of ICIs in recent years [6]. Describing neurological irAEs is necessary not only to promptly adjust therapy in cancer patients but also to accumulate knowledge for the medical community.

In this article, we present two case reports of dysimmune neuropathy that occurred during the treatment with pembrolizumab and nivolumab in patients with metastatic skin melanoma. Chronic inflammatory demyelinating polyneuropathy (CIDP) is usually associated with other causes such as respiratory viral infections, surgery, pregnancy, vaccination, etc. In our cases, PD-1 inhibitors triggered immune response, which resulted in CIDP.

Case report 1

Patient F., 73 years old, received 10 infusions of nivolumab 3 mg/kg in a total dose of 2610 mg for head and neck skin melanoma. First symptoms (i.e. burning sensation in the feet) appeared after the 9th infusion. Within 1.5 months after the 10th infusion, the patient complained of hand pain and leg weakness. Nivolumab was discontinued. Four months after the last infusion, the patient was unable to ambulate and could not turn over in bed without assistance. Examination showed flaccid tetraparesis with plegia in the feet, no tendon reflexes, hypoesthesia of pain sensitivity in the hands, in the legs from the knee level, no vibration sensitivity, atrophy of the distal and proximal arm and leg muscles.

Nerve conduction study (NCS) using Neurosoft 4 MVP micro at a temperature of at least 32°C showed no sensory and motor responses from the lower limbs; unidirectional changes in the upper limbs, i.e. low-amplitude M-responses with conduction velocity decreased to 27 m/s (normal range: more than 50 m/s); and temporal dispersion of the response in the median nerve increased by 68% (Fig. 1). Sensory responses from the hands were not recorded. Needle electromyography (EMG) showed vigorous spontaneous denervation activity in lower leg and forearm muscles and moderate activity in proximal limb muscles. Clinical findings, NCS and EMG parameters were consistent with CIDP [7]. Routine blood tests did not show any abnormalities, and lumbar puncture data were not available because the patient refused to undergo this procedure. The patient was administered methylprednisolone 80 mg/day for 1 month followed by tapering-off and pregabalin 600 mg/day for neuropathic pain syndrome. During the treatment, consistent improvements were seen in foot extension, which improved to Medical Research Council (MRC) score of 3 [8].

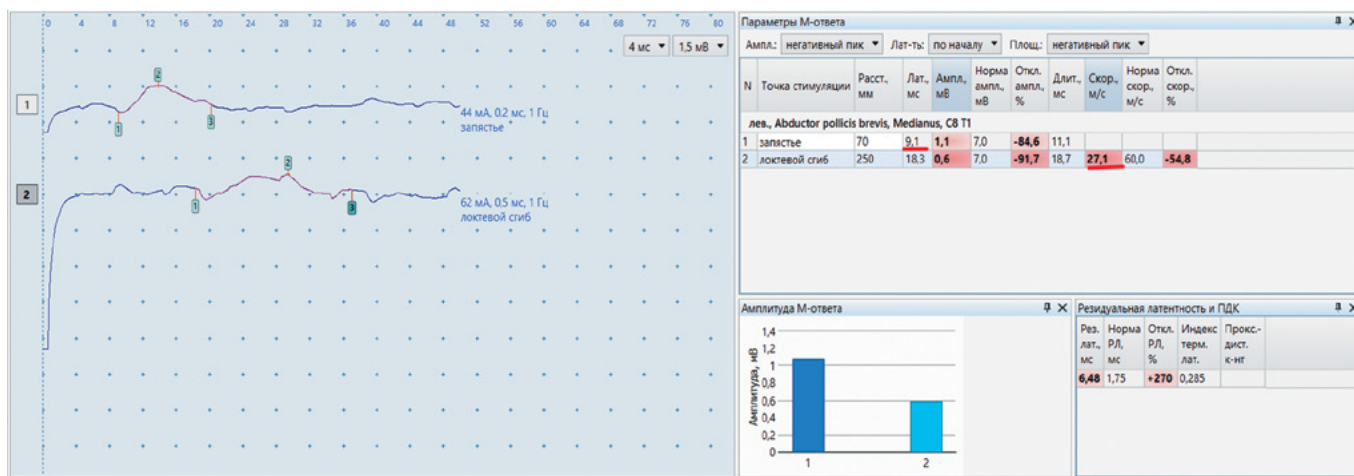


Fig. 1. Decreased conduction velocity in the median nerve in the forearm of patient F. to 27.1 m/s (normal range: > 49 m/s), prolonged distal latency to 9.1 ms (normal range: < 4.4 ms). Negative phase of proximal motor response lasted 18.7 ms. Dispersion of proximal motor response. Amplitude of distal motor response decreased to 1.1 mV (normal range: > 4 mV).

Case report 2

Patient S., 85 years old, received pembrolizumab (2 mg/kg) for skin melanoma of the anterior chest wall with metastases to the lungs, left breast, and postoperative scars. The patient received a total of 5 infusions in a total dose of 1000 mg. First symptoms appeared 2 weeks after the 4th infusion; they included pain in the muscles of the thighs and lower back with Visual Analogue Scale scores of up to 6, which lasted for 1 week. After the 5th pembrolizumab infusion, feet burning sensation and paresthesia appeared with tetraparesis gradually developing. The patient presented with mild dysarthria, areflexia, peripheral tetraparesis with muscle strength decreased to MRC score of 3 in the distal muscles of the arms and legs and to MRC score of 2 in the hip flexors [8]. He had paretic gait with a walker. He lost all sensitivity types in the upper and lower limbs of polyneuritic type (up to knees and up to the middle of the forearm); hyperalgesia of the hands and feet was seen.

Routine laboratory tests showed creatine phosphokinase (CPK) increased to 871 U/L and protein-cell dissociation in the cerebrospinal fluid (cytosis 6 cells/mm³, protein 2.019 g/L). NCS with Dantec Keypoint Focus at a temperature of at least 32°C showed demyelination signs that met the criteria for CIDP [7].

An example of conduction block in an atypical area in the ulnar nerve is shown in Fig. 2. Needle EMG showed single spontaneous activity and minimal neurogenic changes in motor unit potential parameters in the distal muscles of the lower limbs. Brain MRI did not show any significant abnormalities. The patient received 1 session of plasmapheresis with exchanged plasma volume of 35 mL/kg, which was tolerated without complications. However, he experienced general weakness, so further sessions were

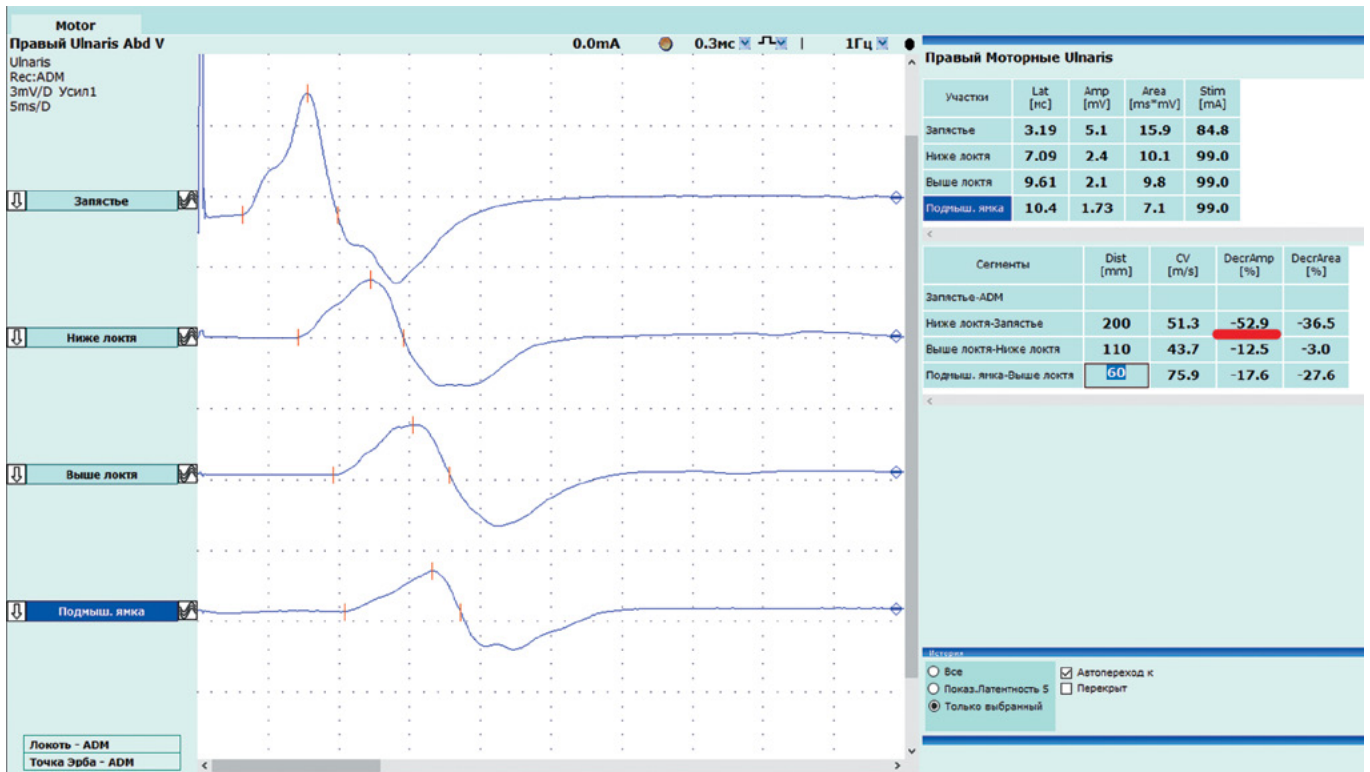


Fig. 2. Conduction block of 52.9% (normal range: no block) in an atypical area of compression in the ulnar nerve. Amplitude of distal motor response decreased to 5.1 mV (normal range: > 6.0 mV). Distal latency was 3.19 ms (normal range: < 3.3 ms).

Summarized patients' data

Parameter	Patient F.	Patient S.
Age, years	73	85
Sex	Male	Male
ICI agent	Nivolumab	Pembrolizumab
Number of infusions	10	5
Total dose, mg	2610	1000
Time to onset, weeks	18	4
NCS	Nerve conduction velocity decreased by 30% in more than 2 nerves	Conduction block of more than 50% in the ulnar nerve, lack of F-wave in the tibial nerves
Needle EMG	Spontaneous activity ++, neurogenic type of changes in motor unit potentials	Spontaneous activity +, minimal neurogenic changes
Treatment	Corticosteroids	Plasmapheresis, corticosteroids

not performed. Oral prednisolone was added with an alternating dosing regimen of 70/35 mg for 4 months, which was associated with a slight improvement with increased strength in the hip flexors and more stable gait. Other neurological parameters remained unchanged. CPK levels returned to normal with the treatment.

Summarized patients' data are presented in the Table.

Discussion

We described two rare cases of CIDP dysimmune neuropathy, which developed after the use of ICIs. According to literature, peripheral nervous system damage occurred 2–5 times more often than complications from the central nervous system [8]. A systematic review by A. Johansen et al. included 61 publications on 85 patients treated with PD-1 inhibitors that were identified from selected indexed literature databases until June 2018, and neuropathy was identified in 23% of cases. The authors noted many cases with atypical presentation, which included combinations of myasthenia gravis and myopathy, as well as common cardiac/respiratory complications, proximal weakness (35%) and muscle pain (28%), which was seen at the onset of the case in patient S. Describing and discussing such cases of ICI complications is important for neurological practice, since mortality in these patients remains high despite adequate treatment, including corticosteroids and intravenous immunoglobulins [9].

Mean time to onset of neurological complications was about 12 weeks after the initiation of ICI therapy [10]. In our patients it was different: 18 weeks in case 1 (after the 9th infusion of nivolumab every 2 weeks) and 14 weeks in case 2 (2 weeks after the 4th infusion of pembrolizumab every 3 weeks).

According to a post-marketing 10-year analysis of the European Pharmacovigilance Database conducted in 2023 and presented by R. Ruggiero et al., all peripheral neuropathies that were the most commonly associated with nivolumab and pembrolizumab included only 12 cases of CIDP. Dysimmune neuropathies included different clinical variants such as Miller–Fisher syndrome, acute inflammatory demyelinating polyneuropathy, etc. Cases of ICI-induced CIDP were reported much less often [11]. A publication suggested that melanoma patients may have a higher risk of developing ICI-induced demyelinating polyneuropathy due to epitopes shared by melanocytes and Schwann cells, as they are both derived from the neural crest [12].

In our cases, clinical findings included symmetrical tetraparesis with sensory impairment. According to literature data, the most typical manifestation of dysimmune neuropathies included symmetrical limb weakness (94% of cases), fol-

lowed by cranial nerve involvement and bulbar disorders [9]. In both our cases, we found demyelinating neuropathy with secondary axonal changes. According to literature, patterns included demyelination (61%) and axonal (27%) patterns [10]. CSF test results were available only for patient S.; they showed protein-cell dissociation. Cerebrospinal fluid showed elevated protein levels in most patients (97%) with lymphocytic pleocytosis in 13 (36%) patients [13]. We did not have any data on anti-ganglioside antibodies in our patients; however, according to the literature, antibodies were positive only in 2 of 17 patients examined [13]. Facial nerve palsy and trigeminal neuralgia were the most frequently noted cranial neuropathies attributed to immune checkpoint inhibitors [14]. No cranial nerve involvement was found in our cases. Small-fiber/autonomic neuropathy was also reported, resulting in orthostasis, anhidrosis, gastrointestinal motility disorders and/or urinary retention [15], which was not seen in our patients. Predominantly demyelinating nature of polyneuropathy induced by ICIs differentiates it from axonal polyneuropathy that occurs in patients who receive conventional chemotherapy [16].

In our cases, ICI-induced CIDP was seen together with neuropathic pain syndrome, which occurred at the onset of the case in patient F. and after resolution of muscle pain in patient S. This was described as a unique manifestation and an early symptom of CIDP in 2 clinical cases when ipilimumab was used in combination with nivolumab in patients with metastatic melanoma [17] and is not typical for classical CIDP.

Causes of neurological irAEs in individual patients are unknown; recently, immunotoxicity has been increasingly associated with changes in the intestinal microbiome [18]. It is of interest that CPK levels in patient S. were increased, which was previously described only in 3 patients with CPK levels of above 1000 U/L with overlap syndromes together with myasthenia, polyneuropathy, and myositis [10]. Most often, increased CPK levels were seen in patients with isolated myositis or a combination of myositis and myasthenia [19]. However, we could not confirm myositis in patient S. because no ongoing process was found in his proximal muscles, and when studied over time, CPK returned to normal quite rapidly, which rather confirms that these changes were of random nature. It remains debatable whether treatment of neurological irAEs can suspend the effectiveness of cancer immunotherapy, thus requiring monitoring over time in this population.

Conclusion

Although ICI-induced neurological complications are rare, they can be serious or even life-threatening; therefore, patients should be continuously monitored during this

treatment. A history of ICI therapy and changes in NCS are the main diagnostic criteria in these cases. Our cases and cases reported in literature supported the hypothesis that compact myelin proteins are likely to be the primary target in ICI-associated neuropathy, particularly in that induced by PD-1-inhibitors. ICI-induced dysimmune neuropathies cannot be discriminated from classic dysimmune

neuropathies by their clinical or neurophysiological signs, with the latter being associated with neuropathic pain. Further studies of these signs in larger cohorts of patients are needed. Key treatment options for neurological irAEs include ICI discontinuation with administration of other therapy based on the decision of the oncology team and prescription of immunosuppressive therapy [20].

References / Список источников

1. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat. Commun.* 2020;11(1):3801. DOI: 10.1038/s41467-020-17670-y
2. Twomey J.D., Zhang B. Cancer Immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. *AAPS J.* 2021;23(2):39. DOI: 10.1208/s12248-021-00574-0
3. Cuzzubbo S., Javeri F., Tissier M. et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. *Eur. J. Cancer.* 2017;73:1–8. DOI: 10.1016/j.ejca.2016.12.001
4. Sharma P., Allison J.P. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell.* 2015;161(2):205–214. DOI: 10.1016/j.cell.2015.03.030
5. Xu M., Nie Y., Yang Y. et al. Risk of neurological toxicities following the use of different immune checkpoint inhibitor regimens in solid tumors: a systematic review and meta-analysis. *Neurologist.* 2019;24(3):75–83. DOI: 10.1097/NRL.0000000000000230
6. Johnson D.B., Manouchehri A., Haugh A.M. et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. *J. Immunother. Cancer.* 2019;7(1):134. DOI: 10.1186/s40425-019-0617-x
7. Van den Bergh P.Y.K., van Doorn P.A., Hadden R.D.M. et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. *J. Peripher. Nerv. Syst.* 2021;26(3):242–268. DOI: 10.1111/jns.12455
8. Супонева Н.А., Арестова А.С., Мельник Е.А. и др. Валидация шкалы суммарной оценки мышечной силы (MRC sum score) для использования у русскоязычных пациентов с хронической воспалительной демиелинизирующей полинейропатией. *Нервно-мышечные болезни.* 2023;13(1):68–74. Suponeva N.A., Arestova A.S., Melnik E.A. et al. Validation of the Medical Research Council sum score (MRCss) for use in Russian-speaking patients with chronic inflammatory demyelinating polyneuropathy. *Neuromuscular Diseases.* 2023;13(1):68–74. DOI: 10.17650/2222-8721-2023-13-1-68-74
9. Khan E., Shrestha A.K., Elkhooly M. et al. CNS and PNS manifestation in immune checkpoint inhibitors: a systematic review. *J. Neurol. Sci.* 2022;432:120089. DOI: 10.1016/j.jns.2021.120089
10. Johansen A., Christensen S.J., Scheie D. et al. Neuromuscular adverse events associated with anti-PD-1 monoclonal antibodies: systematic review. *Neurology.* 2019;92(14):663–674. DOI: 10.1212/WNL.00000000000007235
11. Puwanant A., Isfort M., Lacomis D. et al. Clinical spectrum of neuromuscular complications after immune checkpoint inhibition. *Neuromuscul. Disord.* 2019;29(2):127–133. DOI: 10.1016/j.nmd.2018.11.012
12. Ruggiero R., Balzano N., Di Napoli R. et al. Do peripheral neuropathies differ among immune checkpoint inhibitors? Reports from the European post-marketing surveillance database in the past 10 years. *Front. Immunol.* 2023;14:1134436. DOI: 10.3389/fimmu.2023.1134436
13. Van Raamsdonk C.D., Deo M. Links between Schwann cells and melanocytes in development and disease. *Pigment Cell Melanoma Res.* 2013;26(5):634–645. DOI: 10.1111/pcmr.12134
14. Okada K., Seki M., Yaguchi H. et al. Polyradiculoneuropathy induced by immune checkpoint inhibitors: a case series and review of the literature. *J. Neurol.* 2021;268(2):680–688. DOI: 10.1007/s00415-020-10213-x
15. Dubey D., David W.S., Amato A.A. et al. Varied phenotypes and management of immune checkpoint inhibitor-associated neuropathies. *Neurology.* 2019;93(11):e1093–e1103. DOI: 10.1212/WNL.00000000000008091
16. Kelly Wu W., Broman K.K., Brownie E.R., Kauffmann R.M. Ipilimumab-induced Guillain-Barre syndrome presenting as dysautonomia: an unusual presentation of a rare complication of immunotherapy. *J. Immunother.* 2017;40(5):196–199. DOI: 10.1097/CJI.0000000000000167
17. Тихонова О.А., Дружинин Д.С., Тынтерова А.М., Реверчук И.В. Современное представление о химиоиндуцированной полинейропатии (обзор литературы). *Нервно-мышечные болезни.* 2023;13(1):10–21. Tikhonova O.A., Druzhinin D.S., Tynterova A.M., Reverchuk I.V. Current understanding of chemotherapy-induced peripheral neuropathy. *Neuromuscular Disease.* 2023;13(1):10–21. DOI: 10.17650/2222-8721-2023-13-1-10-21
18. Patel A.S., Snook R.J., Sehdev A. Chronic inflammatory demyelinating polyradiculoneuropathy secondary to immune checkpoint inhibitors in melanoma patients. *Discov. Med.* 2019;28(152):107–111.
19. Elkrief A., Derosa L., Zitvogel L. et al. The intimate relationship between gut microbiota and cancer immunotherapy. *Gut Microbes.* 2019;10(3):424–428. DOI: 10.1080/19490976.2018.1527167
20. Cappelli L.C., Gutierrez A.K., Bingham C.O. et al. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. *Arthritis Care Res. (Hoboken).* 2017;69(11):1751–1763. DOI: 10.1002/acr.23177
21. Brahmer J.R., Abu-Sbeih H., Ascierto P.A. et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J. Immunother. Cancer.* 2021;9(6). DOI: 10.1136/jitc-2021-002435

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