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Encephalomyeloneuritis and arthritis after treatment with immune checkpoint inhibitors

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Abstract

Objective

Immunotherapy revolutionized melanoma treatment; however, immune-related adverse events, especially neurotoxicity, may be severe and require early and correct diagnosis as well as early treatment commencement.

Methods

We report an unusual severe multiorgan manifestation of neurotoxicity after treatment with the anti-PDL1 immune checkpoint inhibitor, nivolumab, and the anticytotoxic T-lymphocyte-associated antigen 4 immune checkpoint inhibitor, ipilimumab, in a 47-year-old male patient with metastatic melanoma.

Results

The patient developed immune-mediated synovitis and cranial neuritis, followed by longitudinal transverse myelitis, encephalitis, and optic neuritis. Early treatment with high-dose steroids and maintenance therapy with rituximab resulted in a favorable neurologic outcome.

Conclusions

The frequency of spinal cord involvement and neuronal toxicity after cancer immunotherapy is very low and requires an extensive diagnostic workup to differentiate between disease progression and side effects. Immune checkpoint inhibitors should be discontinued and treatment with corticosteroids should be initiated early as the drug of first choice. Therapy may be escalated by other immune-modulating treatments, such as rituximab.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

Parts of the case have been presented in a book chapter "Cancer immunotherapy and spinal toxicity."

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Glossary

AQP4 = aquaporin-4; **CE** = contrast enhancing; **CTLA-4** = cytotoxic T-lymphocyte–associated antigen 4; **irAE** = immune-related adverse event; **MP** = methylprednisolone; **NMOSD** = neuromyelitis optica spectrum disease; **ON** = optic neuritis; **PD-1** = programmed death 1; **TM** = transverse myelitis.

We report the case of a 47-year-old male patient diagnosed with metastatic melanoma (T3a N1a M0, stage IIIB, tumor thickness 2.2 mm, Clark Level IV) on his back in July 2017. The molecular histology was BRAFV600E-positive and N-RAS-negative. Sentinel node biopsy was positive, requiring axillary lymphnode dissection. From September 2017, he was put on adjuvant therapy with interferon 2α therapy. In May 2018, lymph node and subcutaneous metastatic lesions were detected (T3a N3c M0, stage IIIC) and treatment with nivolumab 3 mg/kg IV was initiated in July 2018. In February 2019 (after 13 cycles of nivolumab), the disease progressed with new lymph node and subcutaneous metastases. Consequently, in March 2019, immunotherapy was switched to ipilimumab 3 mg/kg IV every 3 weeks.

After the third ipilimumab infusion, the patient developed pain in his left knee and because an immune-mediated synovitis was diagnosed, therapy with ipilimumab was stopped. Fourteen days later, he developed a right-sided peripheral facial palsy. MRI showed enhancement of the cranial nerves (figure 1A), the cervical nerve roots C2/C3, and the cauda equine. CSF analysis revealed elevated protein (110 mg/dL), normal glucose, and mild pleocytosis (40 cells/μL), with lymphocytic activation;[1] IgG index was within the normal range, figure 2. In 3 consecutive lumbar punctures, each with an interval of 2 weeks between no malignant cells were detected, the imaging findings were interpreted to be immune-mediated, and the patient was put on methylprednisolone (MP) 80 mg orally per day with tapering doses. After steroid treatment, the facial palsy recovered completely. Five weeks later, the cranial follow-up MRI scan revealed subependymal and nodular parenchymal contrast-enhancing (CE) lesions without clinical deterioration (figure 1B). CSF analysis showed improvement, so the presumptive diagnosis was a dual pathology with metastatic subependymal tumor spread and immune-related side effects. The tumor board decision was to switch therapy to a BRAF/mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor treatment. A month later, the patient presented acutely to the emergency department complaining of weakness and paresthesias in both legs with progressive immobility and a high grade paraparesis as well as urinary retention and fecal incontinence. He also reported a blurred vision showing a loss of visual acuity to 0.25 on the left eye and an exacerbation of rheumatological condition affecting the ankle joints and the knee. Steroid dose at this time point was MP 20 mg. Cerebral and spinal MRI showed an extensive T2-hyperintense signals and CE of the entire spinal cord and progressive periventricular lesions with CE (figures 1B and 3A). In contrast to these findings, the CE of the cranial nerves was regressive. A repeated CSF analysis revealed increasing pleocytosis (120 leukocytes/μL, predominantly lymphocytes); no malignant cells were detected by CSF cytology. Oligoclonal bands and serum antiaquaporin-4 (AQP4) and antimyelin oligodendrocyte glycoprotein antibodies were negative. Whole body fluorodeoxyglucose-PET/CT showed no evidence for tumor progression.

Based on these findings, an immune-mediated encephalomyelitis with optic neuritis (ON) was diagnosed and the patient was put on high dose IV MP with 1 g for 5 consecutive days, whereas BRAF/MEK inhibitors were continued. Consequently, his neurologic condition, including vision and spinal symptoms, MRI (figures 1C and 3B), and CSF findings (protein 35 mg/dL, 55 cells/μL) markedly improved within 2 weeks. Owing to relapsing disease despite 20 mg MP and a steroid-induced diabetes mellitus, rituximab treatment (1,000 mg total dose, 2 times with an interval of 14 days) was initiated in July 2019. At the last visit in April 2020, the patient showed complete neurologic recovery and complete regression of the imaging findings, but still active arthritis affecting both ankles requires treatment with methotrexate. CSF analysis is within normal limits except for oligoclonal bands which were detected in October 2019 for the first time, IgG Index stayed within normal range. A follow-up PET scan documented a complete resolution of all tumor lesions, and BRAF/MEK inhibitors were stopped after 4 months therapy. Currently (April 2020), the patient is without melanoma treatment.

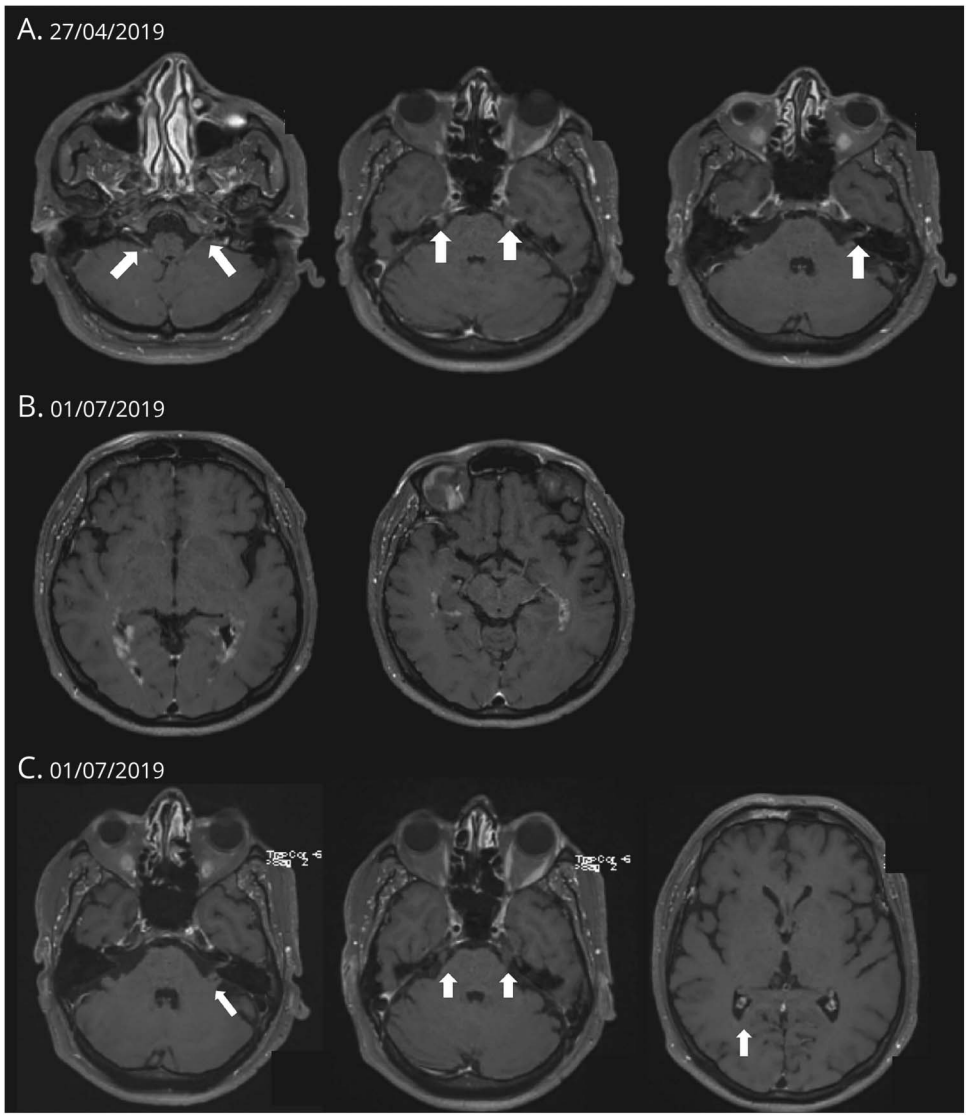
Discussion

The manifestation of different organ systems of immune-related adverse events (irAEs) at different time points makes this case very instructive.

First, after the third ipilimumab infusion, an immune-mediated synovitis was diagnosed and exacerbated after BRAF/MEK inhibitor treatment. Because musculoskeletal irAEs may last up to 1 year,[2] these side effects may subside deferred to the initiation of rituximab treatment.

Two weeks afterward, our patient developed cranial neuritis, which responded very well to oral steroids, but was rapidly complicated by longitudinal extensive transverse myelitis (TM), encephalitis, and ON. In general, neurologic side effects following immune checkpoint inhibitor and BRAF/MEK inhibitor treatment are rare, occurring in <1% of

Figure 1 Cerebral MRI



(A) T1-contrast enhanced images show a contrast enhancement of the 12th and fifth cranial nerve as well as the geniculate ganglion. (B) A follow-up MRI scan revealed subependymal and nodular parenchymal contrast-enhancing (CE) lesions. (C) The cranial MRI scan after high-dose corticosteroid treatment shows complete disappearance of all CE lesions.

patients in large clinical trials.[3] However, a recent evaluation of 59 trials reported a higher incidence of 3.8% in patients receiving anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies, 6.1% in patients receiving anti-programmed death 1 (PD-1) antibodies, and 12% in patients receiving combination therapies,[4] questioning the possibility of a cumulative effect of consecutive immune checkpoint inhibitor treatments, followed by BRAF/MEK inhibitors in the pathophysiology of neurologic adverse effects. It has been suggested that BRAF/MEK inhibition might upregulate inflammatory genes in macrophages and T cells and synergize PD-1 blockade.[5] Given that this new symptoms appeared 1 month after the most recently introduced BRAF/MEK treatment, the possibility of an additive neurotoxic ocular adverse effect[6] and worsening of ankle and knee pain from these treatments has to be considered.[7–9] However, BRAF/MEK inhibitors were not stopped and recovery occurred during treatment with these agents.

Most neurologic complications involve the peripheral nervous system rather than the CNS. Central inflammation is rare and includes, in addition to typical demyelination, several antibody-mediated and paraneoplastic conditions such as anti-NMDA receptor encephalitis.[10] A recent review[11] on irAEs and neurotoxicity including 29 articles encompassing 38 patients identified 11 patients with CNS toxicity. TM has only been reported in 5 cases so far (table e-1, links.lww.com/NXI/A268).

IrAEs occur when T-cell activation exceeds its normal range and induces inflammation.[12] The pathophysiologic pathway remains only partially understood, but immune checkpoints play an important role in immune homeostasis, preventing autoimmunity and promoting self-tolerance. Ipilimumab is directed against CTLA-4, whereas nivolumab and pembrolizumab are directed against PD-1.[13] Inherent to the mechanism of action, these agents upregulate immunity by blocking inhibitory T-cell receptors enhancing antitumor immunity.[14] It is known that

Figure 2 Timeline of symptoms

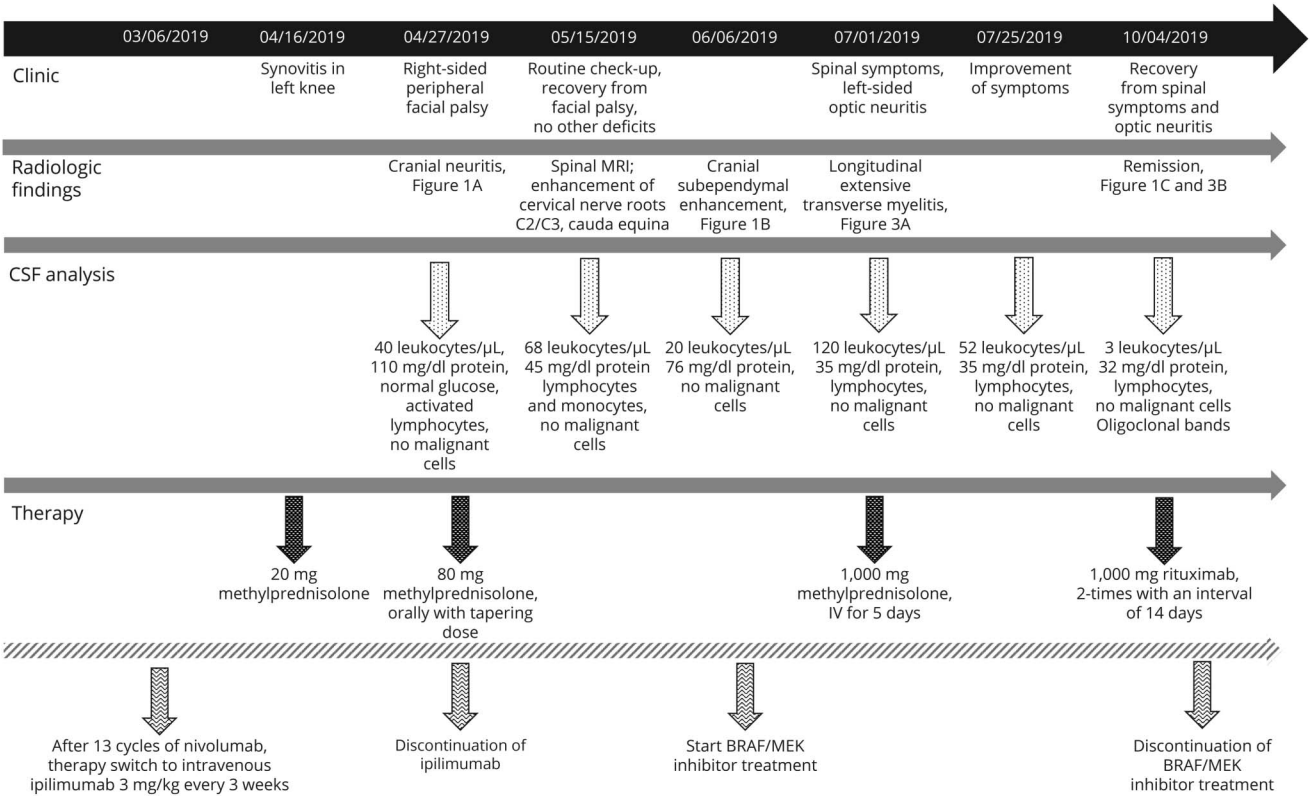
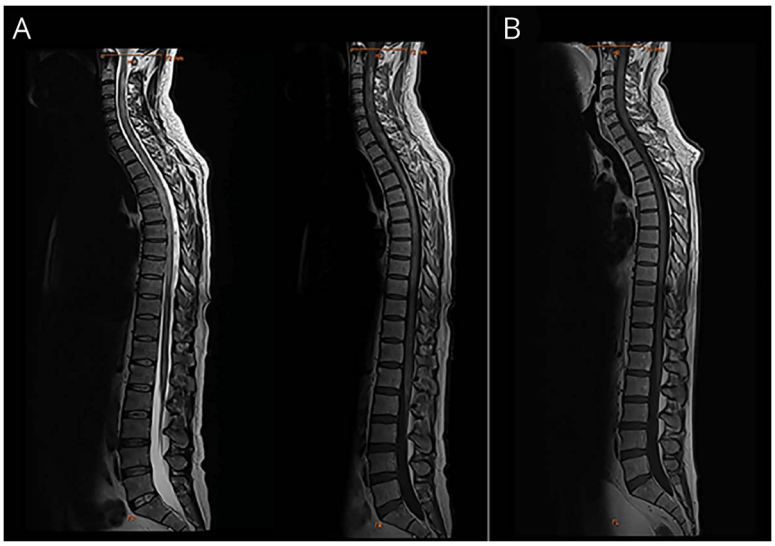


Figure 2 provides a timeline of symptoms, CSF, and radiologic findings.

both PD-1 and CTLA-4 inhibition can stimulate antibody production leading to antibody-mediated autoimmune diseases, especially in patients with pre-existing autoimmunity or autoimmune susceptibility.[15]

Rapid diagnosis and treatment initiation are crucial because severe neurologic sequelae can result from spinal neurotoxicity. A thorough and periodic neurologic examination, a spinal MRI, usually complemented by cerebral MRI, blood

Figure 3 Spinal MRI



(A) Spinal MRI shows extensive T2-hyperintense signal and contrast enhancement of the entire spinal cord. (B) Recovery of all lesions after high-dose corticosteroid treatment.

laboratory analysis (including HIV, rapid plasma regain test, vitamin B12, thyroid-stimulating hormone, antinuclear antibodies, Ro/La, and AQP4 antibodies), and CSF studies (including cytology and immunocytological studies) are the cornerstone of diagnostics. We furthermore want to underline that the severe neurologic manifestations (TM and ON) occurred under low doses of steroids (20 mg of MP) and were first detected by MRI. Therefore, a close monitoring, not only clinically but also with CSF analysis and MRI studies during irAEs, is suggested because MRI might show new abnormalities that might precede the appearance of severe clinical manifestations. Consequently, this might give the opportunity of an early therapeutic change, such as reincrease of steroids, slower tapering, or consideration of high-dose IV steroids that might have prevented or decrease the severity of CNS involvement.

The clinical manifestation of TM and ON in our patient may cast suspicion for neuromyelitis optica spectrum disease (NMOSD). The patient however does not meet the revised criteria for NMOSD without AQP4 antibodies because the required imaging findings were not met. Still, the number of reported cases of iatrogenic demyelination of the CNS is on the rise.[11]

Oncologic societies have released guidelines on the treatment of these irAEs. The European Society of Medical Oncology[4] and the American Society of Clinical Oncology guidelines[16] recommend MP 2 mg/kg body weight for moderate toxicity; however, as soon as activities of daily living are affected, high-dose IV MP (1 g, 3–5 days) is recommended and treatment with immune checkpoint inhibitors should be stopped.

In our patient, we administered rituximab because anti-CD20 treatment proved to be particularly beneficial in NMOSD and symptoms occurred after ongoing MP and severe side effects had occurred.

In summary, we present a case with irAEs affecting the musculoskeletal system, the cranial nerves, and the brain and spinal cord in a metastatic melanoma patient treated with nivolumab followed by ipilimumab and BRAF/MEK inhibitors. The frequency of spinal cord involvement and neuronal toxicity in general in cancer immunotherapy is very low and requires an extensive diagnostic workup including MRI, a number of laboratory tests, and CSF analyses to exclude a broad spectrum of differential diagnoses such as meningeosis carcinomatosa. Differentiation between disease progression and side effects may be difficult and treatment decisions should be discussed in a multidisciplinary team. Immune checkpoint inhibitors should be discontinued and treatment with corticosteroids should be initiated early as the drug of first choice. Therapy may be escalated by other immune-modulating treatments, such as rituximab.

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Disclosure

M. Nowosielski, F. Di Pauli, S. Iglseder, M. Wagner, N. Hoellweger, V.A. Nguyen, J. Gruber, and G. Stockhammer report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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Franziska Di Pauli, MD, PhD	Department of Neurology, Medical University Innsbruck, Austria	Case analysis and revised the manuscript for intellectual content
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Michaela Wagner, MD	Department of Radiology, Medical University Innsbruck, Austria	MRI analysis and revised the manuscript for intellectual content
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