



Case Report

Renal cell carcinoma with central nervous system demyelination caused by nivolumab

Toshiki Oka,¹ Yoshiyuki Yamamoto,¹ Yohei Okuda,¹ Toshihisa Asakura,¹ Koji Hatano,¹ Yasutomo Nakai,¹  Masashi Nakayama,¹ Ken-ichi Kakimoto,¹ Fuminobu Sugai² and Kazuo Nishimura¹ 

¹Department of Urology, Osaka International Cancer Institute, and ²Department of Neurology, Otemae Hospital, Osaka, Japan

Abbreviations & Acronyms

CNS = central nervous system
 CT = computed tomography
 CTCAE = Common Terminology Criteria for Adverse Events
 ICI = immune checkpoint inhibitor
 irAE = immune-related adverse event
 IVIG = intravenous immunoglobulin
 MRI = magnetic resonance imaging
 MS = multiple sclerosis
 mPSL = methylprednisolone
 PD-1 = programmed cell death 1
 RCC = renal cell carcinoma

Introduction: Central nervous system demyelination caused by immune checkpoint inhibitors is a very rare condition.

Case presentation: A 65-year-old man who received nivolumab for renal cell carcinoma developed abnormal behavior, such as disagreeable speech and sudden anger. Brain-enhanced magnetic resonance imaging revealed multiple lesions with partial contrast effects in the cerebral white matter. We tentatively diagnosed demyelination caused by nivolumab, and performed steroid pulse therapy twice. After that, his symptoms improved. For the next 2 years, his symptoms did not recur, nor did his cancer progress.

Conclusion: Demyelination caused by immune checkpoint inhibitors can be fatal and requires early diagnosis and treatment.

Key words: demyelination, immune checkpoint inhibitor, immune-related adverse event, nivolumab, renal cell carcinoma.

Keynote message

Although CNS demyelination owing to ICIs is a rare disorder, it causes neurological symptoms and can be fatal. Early diagnosis and treatment are crucial. Steroids may be required, depending on symptoms.

Introduction

Nivolumab, an anti-PD-1 inhibitor, is widely used to treat various cancers, including RCC; however, numerous irAEs have been reported. Neurologic irAEs are relatively rare,¹ especially neurologic irAEs with CNS demyelination. Here, we report an extremely rare case of RCC with CNS demyelination caused by nivolumab.

Case presentation

A 52-year-old man underwent a left nephrectomy in another hospital for left RCC in 2004 (pathological diagnosis unknown). He developed left lung metastases in 2010, and started treatment with interferon- α . Right renal metastasis also appeared in 2010 (Fig. 1a), so he was referred to our hospital and underwent a right partial nephrectomy. Later, he also underwent a left partial pneumonectomy (Fig. 1b,c). The histopathological finding of each excised tissue showed clear cell RCC. In April 2015, he began sunitinib treatment for multiple lung metastases (Fig. 1d,e) (International Metastatic RCC Database Consortium risk group was favorable), but a lumbar spine metastasis was found in February 2016 (Fig. 1f). His medication was switched from sunitinib to axitinib in November 2016. In October 2017, he began taking nivolumab because of the progression of lung metastases and appearance of left hilar lymph node disease (Fig. 1g,h). In January 2018, he received a transarterial embolization for his left hilar lymph node, because of progressive disease. Both the hilar lymph node and lung disease showed durable responses.

Correspondence: Kazuo Nishimura M.D., Ph.D., Department of Urology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan. Email: kazuo.nishimura@oici.jp

How to cite this article: Oka T, Yamamoto Y, Okuda Y *et al.* Renal cell carcinoma with central nervous system demyelination caused by nivolumab. *IJU Case Rep.* 2021; 4: 44–48.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Received 21 July 2020;
 accepted 25 September 2020.
 Online publication 28 October 2020

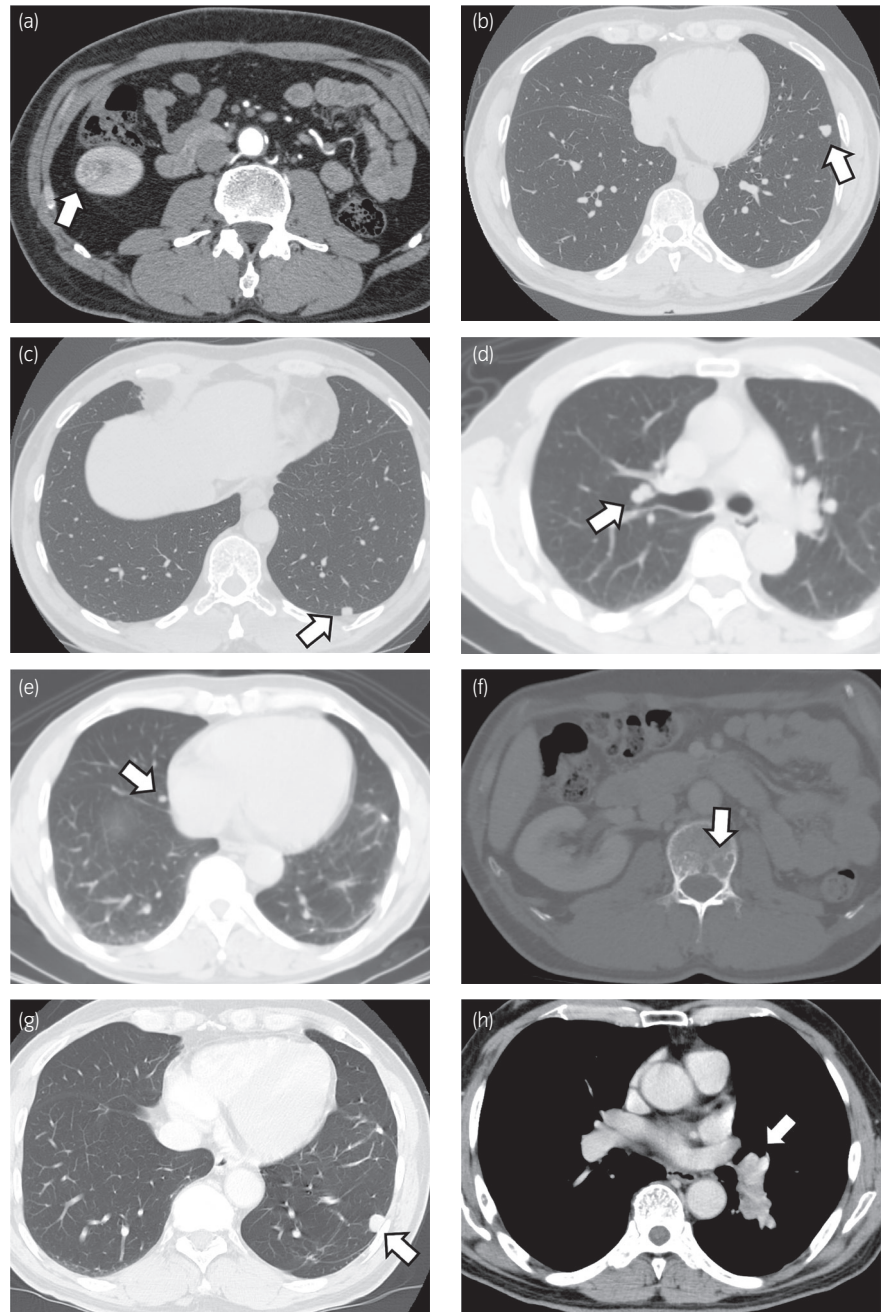


Fig. 1 The CT images are shown. An arrow indicates a metastatic lesion. (a) 16-mm enhanced mass in the lower pole of right kidney; (b) 9-mm coin lesion in the upper lobe of left lung; (c) 8-mm coin lesion in the lower lobe of left lung; (d) 8-mm coin lesion near the hilum of right lung; (e) 5-mm coin lesion in the middle lobe of right lung; (f) 15-mm osteolytic lesion in the second lumbar spine; (g) 13-mm coin lesion in the lower lobe of left lung; (h) 42-mm left hilar lymph node.

Three days after his 11th nivolumab administration, he began displaying abnormal behavior, such as disagreeable speech and sudden anger. Eleven days later, he also developed a short-term memory loss and calculation disorder and was hospitalized on the same day. Brain MRI showed multiple lesions, with high signals in T2-weighted images in his cerebral white matter (Fig. 2a,b). Their open-ring signs suggested demyelination rather than metastatic tumors (Fig. 2c, d). Demyelination caused by nivolumab was considered to be likely, although we need to rule out infectious diseases, collagen diseases, and MS. His cerebrospinal fluid showed normal glucose, protein, and white blood cell count, presence of oligoclonal bands; normal levels of myelin basic protein, immunoglobulin G, and immunoglobulin A for toxoplasma,

and negative JC viral DNA. No malignant cells were found in the cerebrospinal fluid. Most autoantibodies, including anti-aquaporin 4 antibody, were negative except anti-nuclear antibody. On the basis of the above examinations, we diagnosed CNS demyelination caused by nivolumab, which was classified as a grade 2 adverse effect in accordance with the CTCAE version 5.0.

Nivolumab was ceased and intravenous mPSL (1 g/day) was administered for 3 days from the day of his hospital admission. However, as his neurological symptoms did not greatly improve, we began intravenous mPSL (1 g/day) again for 3 days from the eighth day of hospitalization. He then began to show improvement of abnormal behavior as well as imaging findings. Neurological symptoms, such as

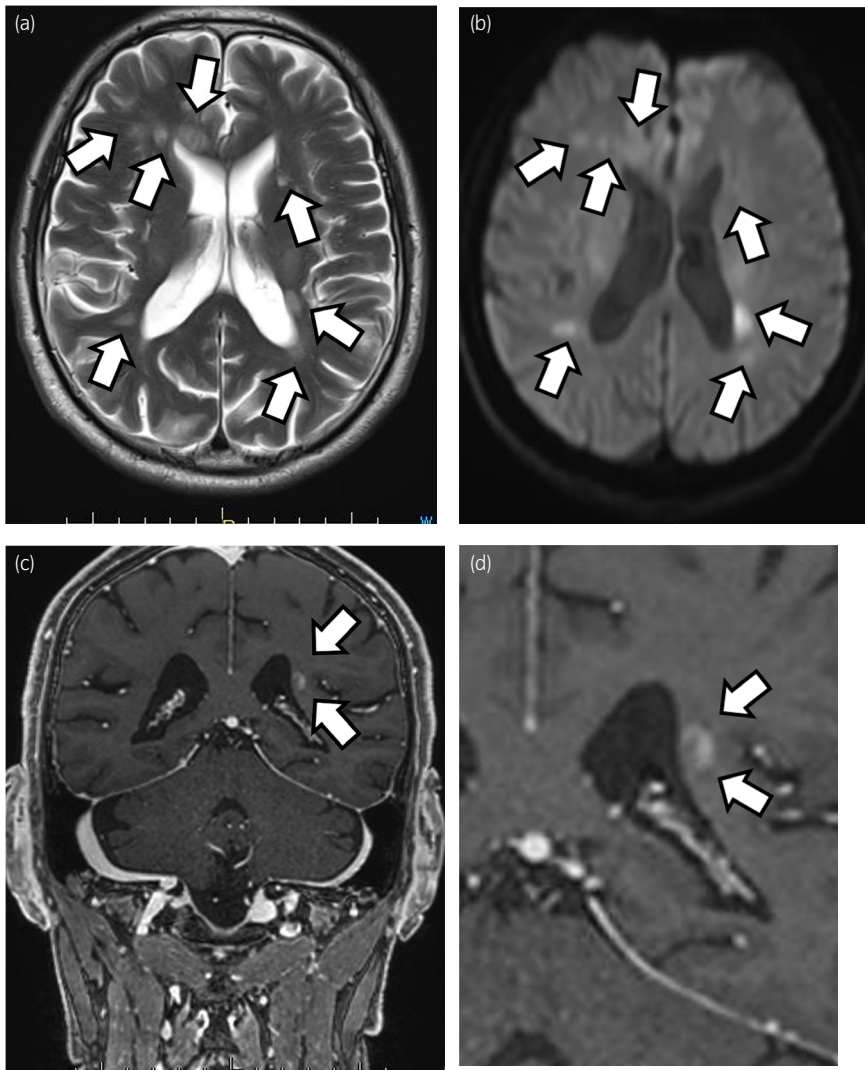


Fig. 2 Brain MRI shows high signal in T2-weighted images and diffusion-weighted images in the cerebral white matter (arrows: CNS demyelination). (a) T2-weighted images; (b) diffusion-weighted images; (c) brain-enhanced MRI shows an open-ring sign; (d) enlarged image of panel c.

disagreeable speech and sudden anger, subsided completely. He was discharged on the 23rd hospital day and fully recovered a short-term memory loss and calculation disorder 3 months after the onset. No steroid was administered other than intravenous mPSL for a total of 6 days. After 6 months, his brain MRI showed further improvement of multiple lesions in the cerebral white matter (Fig. 3). Nivolumab has been discontinued and neither neurologic symptoms nor progression of RCC have been observed for 26 months without any treatment.

Discussion

A report of 9208 patients treated with ICIs, enrolled in 59 clinical trials, showed that 3.8% of patients were treated with cytotoxic T-lymphocyte-associated protein-4 inhibitor, 6.1% of those with PD-1 inhibitor and 12.0% of those with both agents had neurologic irAEs.¹ Yet, neurologic irAEs with CNS demyelination are rare conditions. Neurologic irAEs encompass a broad spectrum of neurologic syndromes, including myasthenic syndrome, aseptic meningitis, encephalitis, sensory motor neuropathy, Guillain-Barré-like

syndromes, painful sensory neuropathy, enteric neuropathy, transverse myelitis, and posterior reversible encephalopathy syndrome.² To diagnose neurologic irAEs, infectious diseases, cancer invasion to CNS, paraneoplastic syndrome, and metabolic disorders must be ruled out. Blood tests that include hormone levels, cerebrospinal fluid tests, and brain-enhanced MRI are essential.³ In patients with CTCAE grade 1 neurologic symptoms, ICIs should be continued under close observation. Among those with CTCAE grade ≥ 2 neurological symptoms, administration of corticosteroids equivalent to mPSL (1–4 mg/kg), and discontinuation of ICIs, or treatment such as IVIG, plasma exchange, and steroid pulse are required depending on severity.²

To our knowledge, only eight cases of CNS demyelination owing to ICIs have been reported, including the present case (Table 1).^{4–10} Our report is the first case of CNS demyelination caused by nivolumab to treat RCC. All other reported patients were treated with steroids except for one patient with no symptoms who was relieved by only discontinuation of nivolumab. IVIG, plasma exchange, and immunosuppressant were added in some cases. In previous reports, most patients with irAEs involving the CNS had onset of symptoms

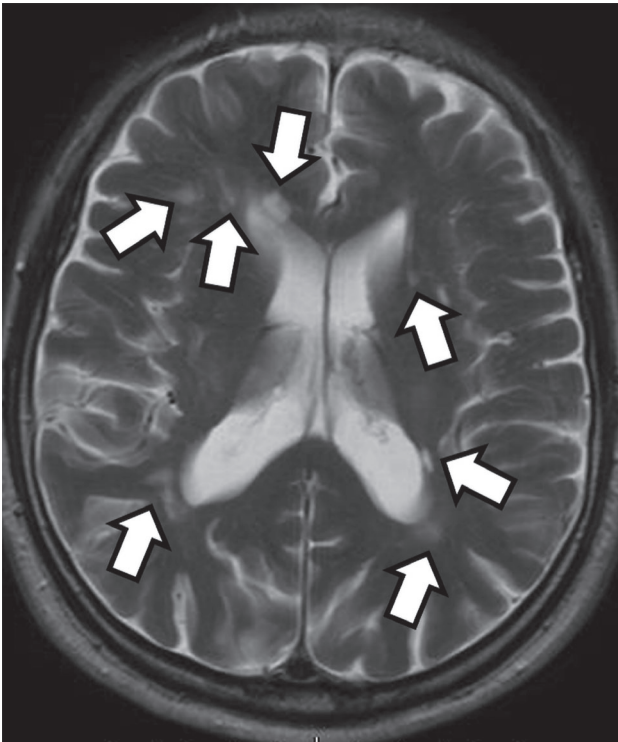


Fig. 3 Brain MRI (T2-weighted images) taken 6 months after discharge showed further improvement of multiple lesions in the cerebral white matter (arrows: CNS demyelination).

<4 days after administering nivolumab, and symptoms became progressively worse within 2 weeks.⁸ Except for one patient with unknown details, all eight patients improved in response to treatment. However, one died from relapsed CNS demyelination, and two died from complications of steroid treatment. As four cases out of eight died, CNS demyelination caused by ICIs can be fatal. We tried the second steroid pulse therapy in the same manner as for MS, which is a CNS demyelinating disease with a clinical picture similar to our case. Since the neurological symptoms were not severe and subsided after the second administration of mPSL, we decided to follow-up carefully without continuing steroid administration.

An autopsy for a patient with CNS demyelination revealed infiltration of CD8⁺ T cells into the margin of the demyelinating lesion.⁴ Furthermore, a pathway in which CD8⁺ T cells damaged the myelin sheath has been reported for MS.¹¹ Furthermore, others have reported that the autopsy of MS patients showed no PD-1 expression by CD8⁺ T cells that infiltrate the lesion site.¹² These facts support the hypothesis that the CD8⁺ T cells whose PD-1 receptors are inhibited by nivolumab may injure the myelin sheath and cause CNS demyelination.

Conclusion

We experienced a case of RCC with demyelination of the CNS owing to nivolumab. Because this condition may be fatal, early diagnosis and treatment are necessary.

Table 1 Review of cases of cerebral nervous system demyelination secondary to treatment with ICIs

| Case | Author/year | Underlying disease | Suspected drug | Symptom | Treatment provided | Responsiveness to treatment | Outcome |
|------|---|----------------------|-------------------------|--|--|------------------------------------|---|
| 1 | Maurice <i>et al.</i> ⁴ /2015 | Melanoma | Nivolumab | Confusion Nausea Vomiting Apathy Fixed gaze Psychomotor slowing | mPSL IVIg | After remission, symptoms reappear | Died due to demyelinating disease |
| 2 | Cao <i>et al.</i> ⁵ /2016 | Melanoma | Ipilimumab | Fatigue Memory loss Vision change | mPSL Cyclophosphamide | Unknown | Died |
| 3 | Sugiura <i>et al.</i> ⁶ /2017 | Lung cancer | Nivolumab | Low motivation Wobbling | mPSL | Improvement | Died due to cytomegalovirus ulcer in the lower intestinal tract |
| 4 | Mancone <i>et al.</i> ⁷ /2018 | Melanoma | Nivolumab Ipilimumab | Gait imbalance Lower extremity weakness | mPSL IVIg | Mild improvement | Died due to urinary tract infection |
| 5 | Zafer <i>et al.</i> ⁸ /2019 | Laryngeal cancer | Nivolumab | Diffuse generalized slowing | mPSL IVIg | Improvement | Survived |
| 6 | Pillonel <i>et al.</i> ⁹ /2019 | Melanoma | Nivolumab | No symptom | Only discontinuation of nivolumab | Improvement | Survived |
| 7 | Duraes <i>et al.</i> ¹⁰ /2019 | Melanoma | Pembrolizumab | Distal numbness of the limbs Weakness with gait impairment | Intravenous steroid Plasma exchange | Improvement | Survived |
| 8 | Our case | Renal cell carcinoma | Nivolumab | Disagreeable speech Sudden anger Memory loss Calculation disorder | mPSL | Improvement | Survived |

Acknowledgment

We thank Marla Brunker, from Edanz Group (<https://en-au-thor-services.edanzgroup.com/>), for editing a draft of this manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

- 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.
- Brahmer J, Lacchetti C, Schneider BJ *et al.* Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J. Clin. Oncol.* 2018; **36**: 1714–68.
- Puzanov I, Diab A, Abdallah K *et al.* Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J. Immunother. Cancer* 2017; **5**: 95.
- Maurice C, Schneider R, Kiehl TR *et al.* Subacute CNS demyelination after treatment with nivolumab for melanoma. *Cancer Immunol. Res.* 2015; **3**: 1299–302.
- Cao Y, Nylander A, Ramanan S *et al.* CNS demyelination and enhanced myelin-reactive responses after ipilimumab treatment. *Neurology* 2016; **86**: 1553–6.
- Sugiura Y, Yutani S, Fujimoto H *et al.* Central nervous system demyelination after treatment with nivolumab for lung cancer: a case report. *Jpn. J. Chest Surg.* 2017; **31**: 717–21.
- Mancone S, Lycan T, Ahmed T *et al.* Severe neurologic complications of immune checkpoint inhibitors: a single-center review. *J. Neurol.* 2018; **265**: 1636–42.
- Zafar Z, Vogler C, Hudali T *et al.* Nivolumab-associated acute demyelinating encephalitis: a case report and literature review. *Clin. Med. Res.* 2019; **17**: 29–33.
- Pillonel V, Dunet V, Hottinger AF *et al.* Multiple nivolumab-induced CNS demyelination with spontaneous resolution in an asymptomatic metastatic melanoma patient. *J. Immunother. Cancer* 2019; **7**: 336.
- Duraes J, Coutinho I, Mariano A *et al.* Demyelinating disease of the central nervous system associated with pembrolizumab treatment for metastatic melanoma. *Mult. Scler.* 2019; **25**: 1005–8.
- Johnson TA, Jirik FR, Fournier S. Exploring the roles of CD8(+) T lymphocytes in the pathogenesis of autoimmune demyelination. *Semin. Immunopathol.* 2010; **32**: 197–209.
- Pittet CL, Newcombe J, Antel JP *et al.* The majority of infiltrating CD8 T lymphocytes in multiple sclerosis lesions is insensitive to enhanced PD-L1 levels on CNS cells. *Glia* 2011; **59**: 841–56.