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Case Report

Pembrolizumab-induced myelitis in stage 4 renal clear cell carcinoma: a case report

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Abstract: Pembrolizumab, an immune checkpoint inhibitor targeting the programmed cell death 1 (PD-1) protein, is widely used for renal cell carcinoma but rarely causes central nervous system adverse events such as myelitis. A 58-year-old woman with stage IV renal clear cell carcinoma developed radiating hip pain, paresthesia, hypoesthesia (T10 and below), constipation, urinary retention, and sudden right-eye blurred vision one month after her sixth cycle of pembrolizumab and lenvatinib. Neurologic examination revealed asymmetrical inferior paraparesis, upper motor neuron signs, and right eye papilledema. MRI demonstrated patchy hyperintensity on C2-C6 and T2-T5, supportive of myelitis. Intravenous methylprednisolone was initiated, leading to pain relief and motor improvement. This is the first reported case of pembrolizumab-induced myelitis in Indonesia, emphasizing the importance of early recognition and corticosteroid therapy for optimal recovery.

Keywords: Pembrolizumab, Immune Checkpoint Inhibitor, Myelitis, Renal Cell Carcinoma

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1. Introduction

With the breakthrough in technology and knowledge, immunotherapies are now more commonly used for cancer treatment. Pembrolizumab is a type of immunotherapy drug called immune checkpoint inhibitor (ICI) and is gaining popularity in the treatment of various cancers, including renal cell carcinoma (RCC). It is a monoclonal antibody that binds to the programmed cell death 1 (PD-1) protein on the surface of T cells. The anti-PD-1 antibody blocks the link between PD-1 and its ligands, allowing cytotoxic T cells to kill tumor cells [1]. A combination of pembrolizumab and tyrosine kinase inhibitors (TKI), such as lenvatinib, is now recommended as first-line treatment for advanced RCC [2]. Pembrolizumab is found to grant significant disease-free survival as an adjuvant therapy for patients with RCC after nephrectomy compared with placebo [3].

Although Pembrolizumab has been found effective, it is associated with several known adverse events affecting various body systems, including gastrointestinal, hepatic, respiratory, and ocular systems. The nervous system is less affected, with less than 5% incidence. On top of that, central nervous system involvement, including myelitis, constructs only 0.5% of the incidence. Myelitis can also happen in conjunction with or before optic neuropathy, another rare complication of Pembrolizumab [4]. Management requires permanent discontinuation of pembrolizumab and administration of steroid or intravenous immunoglobulin [5]. We present a rare case of pembrolizumab-induced myelitis in Indonesia.

2. Case presentation

A 58-year-old woman presented to the emergency department with stabbing hip pain radiating to both feet since one day before admission, with a VAS of 8 – 9. The pain was accompanied by paresthesia and hypoesthesia in the dermatomal distribution of T10 and below. The patient had difficulty walking due to weakness in both legs, more so in the left leg. Constipation and urine retention two days before admission were also reported. The past medical history was remarkable for stage IV left renal clear cell cancer (WHO/ISUP grade 3, T3aN0M1 metastasized to lung) post radical nephrectomy. The patient received six cycles of chemotherapy using 200 mg of Pembrolizumab and 10 – 20 mg of Lenvatinib over six months, with the last cycle done one month before admission. On the fourth day of admission, the patient complained of sudden blurred vision in her right eye.

Physical examination was remarkable for decreased visual acuity in the right eye with VOD 1/60 and negative relative afferent pupillary defect (RAPD) in both eyes. Funduscopy showed papilledema on the right eye. Neurological examination revealed asymmetrical inferior paraparesis 3/2, increased all physiological reflexes, positive Hofman-Tromner test, and positive Babinski pathological reflex. Non-contrast spine magnetic resonance imaging (MRI) disclosed patchy hyperintensity on T2WI with thickening of medulla spinalis on C2-C6 and hyperintensity on T2-T5 supportive of myelopathy, with the possibility of myelitis (Figure 1).

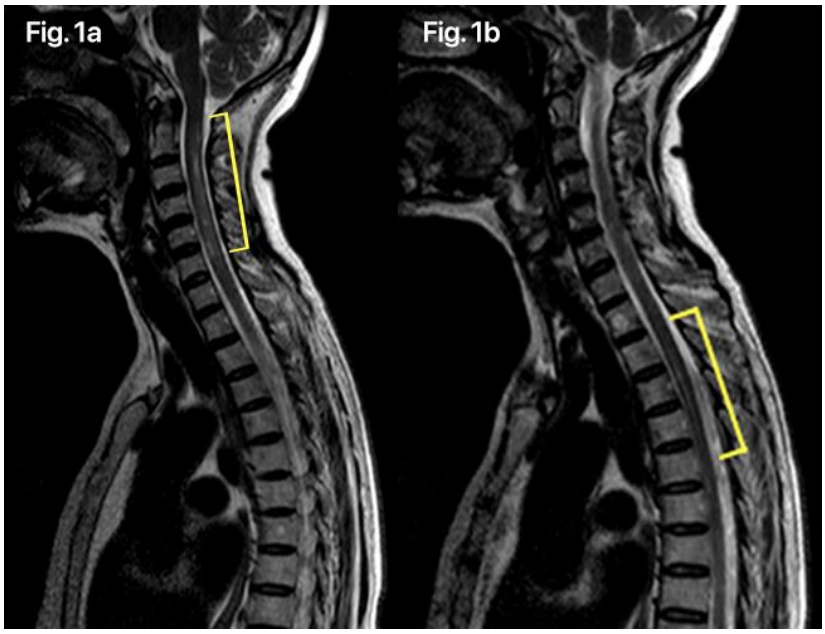

Figure 1. Spine sagittal view on non-contrast T2 weighted MRI. (a) Patchy hyperintensity on C2 – C6. (b) Hyperintensity on T2 – T5

Non-contrast brain MRI found evidence of bilateral papilledema (Figure 2). Contrast imaging was not done due to the patient's poor kidney function. Routine cerebrospinal fluid analysis was normal and clear of malignant cells, eliminating the possibility of infection or intramedullary metastasis. Pleocytosis and increased glucose and protein were reported. A nerve conduction study demonstrated bilateral peroneal, right tibial, median, and ulnar neuropathy with motoric axonal type.

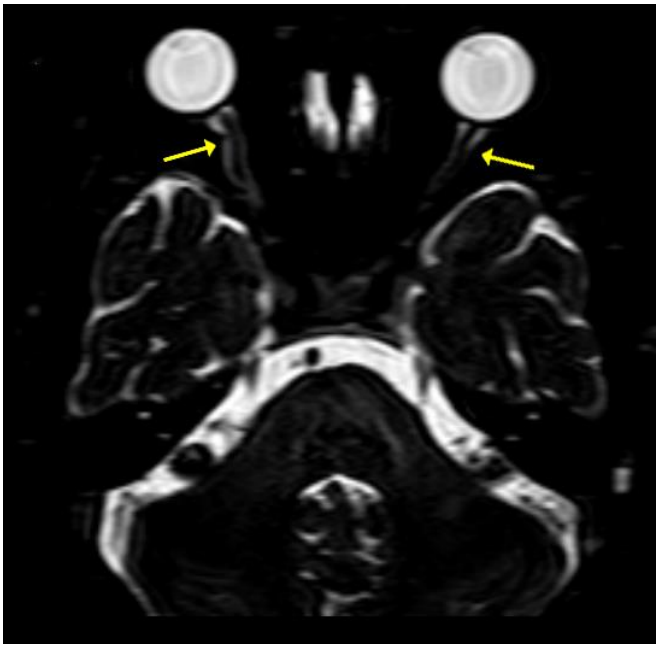

Figure 2. Non-contrast T2 weighted MRI of the brain showing prominent cerebrospinal fluid surrounding bilateral mildly tortuous optic nerves with flattening of bilateral posterior sclera, suggestive of bilateral papilledema

Upon admission, the patient was placed on a foley catheter and treated with 75 mg of pregabalin twice daily for the pain. Following the MRI result, the patient was started on 250 mg methylprednisolone four times daily and then tapered off after five days. The pain was subsequently reduced, but the paresthesia, hypoesthesia, and blurred vision remained. Considering this improvement, administration of IVIG or plasmapheresis was withheld. The patient was discharged after 17 days of hospitalization with 16 mg methylprednisolone four times daily, tapered off every three days, 75 mg pregabalin twice daily, and 500 mcg methylcobalamin three times daily. Motor improvement was noticed during follow-up in the outpatient clinic, enabling the patient to walk without ambulation, with motor power of 4/4.

3. Discussion

Increasing usage of ICIs such as pembrolizumab increases the number of adverse events reported. The incidence of neurological adverse events occurs in less than 5% of patients receiving ICIs, and up to 6.1% of patients treated with anti-PD-1 antibodies, such as pembrolizumab, experience neurological adverse events [4,6]. However, most adverse neurological events occur in the peripheral nervous system and rarely affect the central nervous system. Peripheral nervous system (PNS) adverse events of ICIs span from myositis and myasthenia gravis to peripheral neuropathies, including Guillain-Barre syndrome. Commonly reported central nervous system (CNS) adverse events of ICIs are encephalitis, aseptic meningitis, and multiple sclerosis. Myelitis, vasculitis, and cranial nerve disorder are several rare cases of CNS adverse events of ICIs [4,7]. Although ICI-related neurological adverse events construct only a tiny number of cases, they result in high morbidity and mortality, for about 11% of mortality secondary to ICI is due to neurological adverse events [8], Here, we present the first reported rare case of anti-PD-1 antibody-induced myelitis in Indonesia.

The exact mechanism of anti-PD-1 antibody-induced neurological adverse events is still unknown. It is known that tumor cells express programmed cell death ligand-1 (PDL-1) on its surface, which links with PD-1 on the T cell surface and produces a downregulatory effect on T cell differentiation and proliferation, which will prevent

tumor cell destruction. Pembrolizumab works on inhibiting this linkage so T cells can attack tumor cells. However, this will cause uninhibited T cell proliferation and differentiation and, through unknown mechanisms, can lead to increased responses of Th1 and Th17, increased IL-6 and IL-17 production, and abnormal humoral immunity and Treg activity. Production of autoantibodies can happen due to molecular mimicry between tumor cells and CNS antigens, causing adverse CNS events [9].

Clinical manifestations of myelitis vary from case to case and commonly include paraparesis and sensory and autonomic dysfunction, mirroring the presentation observed in our patient. Sometimes, proprioceptive ataxia may also be evident. Myelitis can also happen in conjunction with or prior to optic neuritis, termed neuromyelitis optica, another rare complication of pembrolizumab [4]. Our patient experienced blurred vision in the right eye, with funduscopy revealing right eye papilledema. This may be attributed to optic neuritis, as some cases of papilledema stem from optic neuritis [10]. However, this diagnosis remains debatable due to the absence of hyperintense lesions in the optic nerve T2 MRI sequence, a hallmark of optic neuritis [11]. A case reported by Nasralla in 2020 showed a similar manifestation to our case, with a 30-year-old woman treated using another type of PD-1 inhibitor, nivolumab, developing neuromyelitis optica. She first experienced paraparesis in the lower extremity, urinary retention, and paroxysmal right tonic spasm, followed by right eye vision loss one month after plasmapheresis and corticosteroid treatment. Nevertheless, her orbital MRI exhibited optic nerve and optic chiasm enhancement, indicative of optic neuritis, contrasting with our patient's case [12].

Management of adverse neurological events generally depends on the grade of the adverse events. However, diagnosis of ICI-induced myelitis of any grade commands for discontinuation of ICI and administration of immune modulators such as methylprednisolone or prednisolone of 2 mg/kg body weight. Some patients should consider a higher dose of 1 g/day for 3 to 5 days. If no improvement is noted, intravenous immunoglobulin (IVIG) or plasmapheresis can be considered [5,13]. According to several case series and research, corticosteroids alone are usually insufficient to alleviate adverse neurological events. 70 – 75% of patients treated using only intravenous corticosteroids experienced relapse or poor recovery of myelitis and needed second-line immunotherapy [14,15]. Our patient responded well to corticosteroids as she was treated using only methylprednisolone and showed a reduction in pain and, later, during an outpatient visit, showed motoric improvement. IVIG or plasmapheresis was not done in consideration of the patient's improvement using corticosteroids and the extent of renal cancer this patient has.

4. Conclusions

We reported a rare case of renal clear cell cancer patient with anti-PD-1 antibody-induced myelitis. To our best knowledge, this is the first reported case in Indonesia. We highlight that although the incidence of anti-PD-1 antibody-induced myelitis is rare, clinicians should always consider this possibility in every patient receiving anti-PD-1 antibody. Early recognition and treatment using immunomodulators such as corticosteroids, IVIG, or plasmapheresis might help patients' clinical recovery.

Supplementary Materials: None

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References

[1] Peters S, Kerr KM, Stahel R. PD-1 blockade in advanced NSCLC: A focus on pembrolizumab. Cancer Treat Rev. 2018 Jan;62:39–49. DOI:10.1016/j.ctrv.2017.10.002

[2] Capitanio U, Fallara G, Raggi D, Nocera L, Larcher A, Belladelli F, et al. Pembrolizumab in advanced renal cell carcinoma: a meta-analysis providing level 1a evidence. Curr Probl Cancer. 2022 Aug;46(4):100875. DOI:10.1016/j.currproblcancer.2022.100875

[3] Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. New England Journal of Medicine. 2021 Aug 19;385(8):683–94. DOI:10.1056/NEJMoa2106391

[4] Albarrán V, Chamorro J, Rosero DI, Saavedra C, Soria A, Carrato A, et al. Neurologic Toxicity of Immune Checkpoint Inhibitors: A Review of Literature. Front Pharmacol. 2022 Feb 14;13. DOI:10.3389/fphar.2022.774170

[5] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology. 2018 Jun 10;36(17):1714–68. DOI:10.1200/JCO.2017.77.6385

[6] Möhn N, Beutel G, Gutzmer R, Ivanyi P, Satzger I, Skripu T. Neurological Immune Related Adverse Events Associated with Nivolumab, Ipilimumab, and Pembrolizumab Therapy—Review of the Literature and Future Outlook. J Clin Med. 2019 Oct 24;8(11):1777. DOI:10.3390/jcm8111777

[7] Haugh AM, Probasco JC, Johnson DB. Neurologic complications of immune checkpoint inhibitors. Expert Opin Drug Saf. 2020 Apr 2;19(4):479–88. DOI:10.1080/14740338.2020.1738382

[8] Farooq MZ, Aqeel SB, Lingamaneni P, Pichardo RC, Jawed A, Khalid S, et al. Association of Immune Checkpoint Inhibitors With Neurologic Adverse Events. JAMA Netw Open. 2022 Apr 19;5(4):e227722. DOI:10.1001/jamanetworkopen.2022.7722

[9] Dalakas MC. Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. Ther Adv Neurol Disord. 2018 Jan 14;11. DOI:10.1177/1756286418799864

[10] Nguyen H, Haider K, Ackerman L. Unusual causes of papilledema: Two illustrative cases. Surg Neurol Int [Internet]. 2013;4(1):60. Available from: http://surgicalneurologyint.com/surgicalint-articles/unusual-causes-of-papilledema-two-illustrative-cases/

[11] Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177–89. DOI:10.1212/WNL.0000000000001729

[12] Nasralla S, Abboud H. Is neuromyelitis optica without AQP4-IgG a T-cell mediated disease? insights from checkpoint inhibitor immune-related adverse events. Mult Scler Relat Disord. 2020 Nov;46:102451. DOI:10.1016/j.msard.2020.102451

[13] Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017 Jul;28:iv119–42. DOI:10.1093/annonc/mdx225

[14] Chatterton S, Xi S, Jia JX, Krause M, Long G V., Atkinson V, et al. Case series: Immune checkpoint inhibitor-induced transverse myelitis. Front Neurol. 2023 Feb 21;14. DOI:10.3389/fneur.2023.1130313

[15] Picca A, Berzero G, Bihan K, Jachiet V, Januel E, Coustans M, et al. Longitudinally Extensive Myelitis Associated With Immune Checkpoint Inhibitors. Neurol Neuroimmunol Neuroinflamm. 2021 May;8(3). DOI:10.1212/NXI.0000000000000967