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LETTER TO THE EDITOR

Low-dose nivolumab induced durable complete response in relapsed primary central nervous system diffuse large B cell lymphoma

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Dear Editor,

Primary central nervous system lymphoma (PCNSL), confined to the brain, spinal cord, and occasionally the eyes [1], is an aggressive malignancy. Standard treatment comprises rituximab and high-dose intravenous methotrexate (HD-MTX), followed by whole-brain radiotherapy (WBRT) or autologous hematopoietic stem cell transplantation (AHSCT) [2]. However, responses are typically short-lasting, with relapse rates of up to 50% [1]. Treatment of relapses remains challenging. Conventional options if not given before, including HD-MTX, WBRT, or AHSCT, result in poor outcome [1]. Other agents including ibrutinib, lenalidomide, and temsirolimus gave variable transient responses (median progression-free survivals, 1.5–8.1 months) [2, 3]. Novel approaches are needed.

Genomic analysis of PCNSL has shown high frequencies of copy number gains in chromosome 9p24.1, which contains the programmed cell death ligand-1 (*PDL1*) and *PDL2* genes [4]. PDL1 and PDL2 are cognate ligands for the inhibitory receptor PD1 on effector T cells. Ligation of PDL1/PDL2 with PD1 inhibits effector T cell function. Over-expression of PDL1/PDL2 in PCNSL thus represents a mechanism of immune evasion. Accordingly, PD1 blockade may be a potential therapeutic strategy.

A 66-year-old man presented with headache and urinary incontinence. Magnetic resonance imaging (MRI) showed multiple lesions in the periventricular white matter of bilateral frontal and parietal lobes and corpus callosum (Fig. 1). Biopsy showed Epstein-Barr virus–negative diffuse large B cell lymphoma of non-germinal center B cell origin (Fig. 2a–c). PDL1 was positive in about 10% of lymphoma cells (Fig. 2d). F18-fluorodeoxyglucose positron emission tomography computed tomography (PET/CT) showed no extra-cranial involvement. Marrow was not involved histopathologically. Overall features were consistent with PCNSL.

Because of liver dysfunction on presentation, HD-MTX was not used. Instead, he was treated with two courses of high-dose cytarabine (each course, 3 g/m^2/day × 2). Reassessment MRI showed marked improvement of the index lesions. Consolidation WBRT was given. One month afterwards, bilateral lower limb weakness developed. MRI showed disease progression in the spinal cord, from the second cervical to the fourth thoracic levels. Radiotherapy followed by six cycles of rituximab and HD-MTX were given, leading to PET/CT-confirmed complete response (CR) of the brain and spinal cord lesions.

One month later, however, he presented with clumsiness. MRI showed suspected relapse at the right lateral ventricle and left occipital horn (Fig. 3a). There was gradual deterioration, and a CT scan four weeks later showed infiltrative lesions in bilateral basal ganglia (Fig. 3a). Dexamethasone (16 mg/day) was started. As there were no standard salvage options, with informed consent, he was given low-dose nivolumab at 40 mg every two weeks (Q2W). After the first dose, clinical improvement was obvious, and dexamethasone was withdrawn. After the second dose, CT scan showed marked improvement (Fig. 3b). After four doses, MRI showed resolution of practically all brain lesions (Fig. 3b).

Nivolumab was continued at 40 mg Q2W in the first year and spaced to 40 mg Q3W in the second year to economize on cost. MRI at nine and sixteen months showed continuous CR. He has since finished two years of treatment (amounting to 41 cycles or a cumulative dose of 1640 mg of nivolumab), remaining in CR clinically and radiologically. No immune-related adverse events (irAE) were observed.

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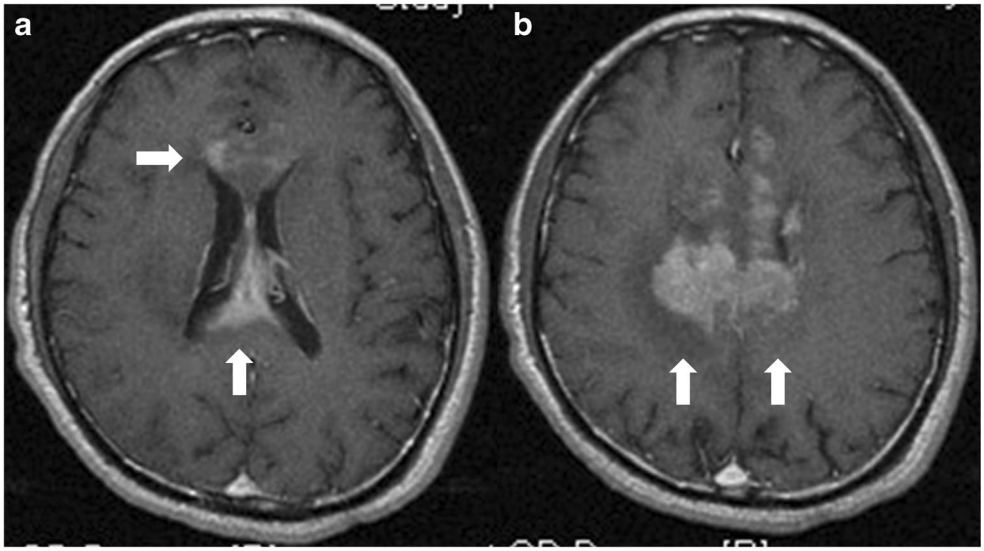

Fig. 1 Lesions on presentation. Post-contrast axial magnetic resonance imaging showing extensive bilateral involvement of periventricular white matter extending across the corpus callosum (arrows, **a** and **b**)

There are some important observations. We showed PD1 blockade to be highly effective for PCNSL. Although at diagnosis PDL1 was positive in only 10% of lymphoma cells, a biopsy was not repeated at relapse. PDL1 expression is dynamic and can be upregulated by tumor cells in an adaptive manner [5]. Hence, a low presentation PDL1 expression might not necessarily correlate with response to PD1/PDL1 blockade at relapse/refractory disease. Treatment with nivolumab

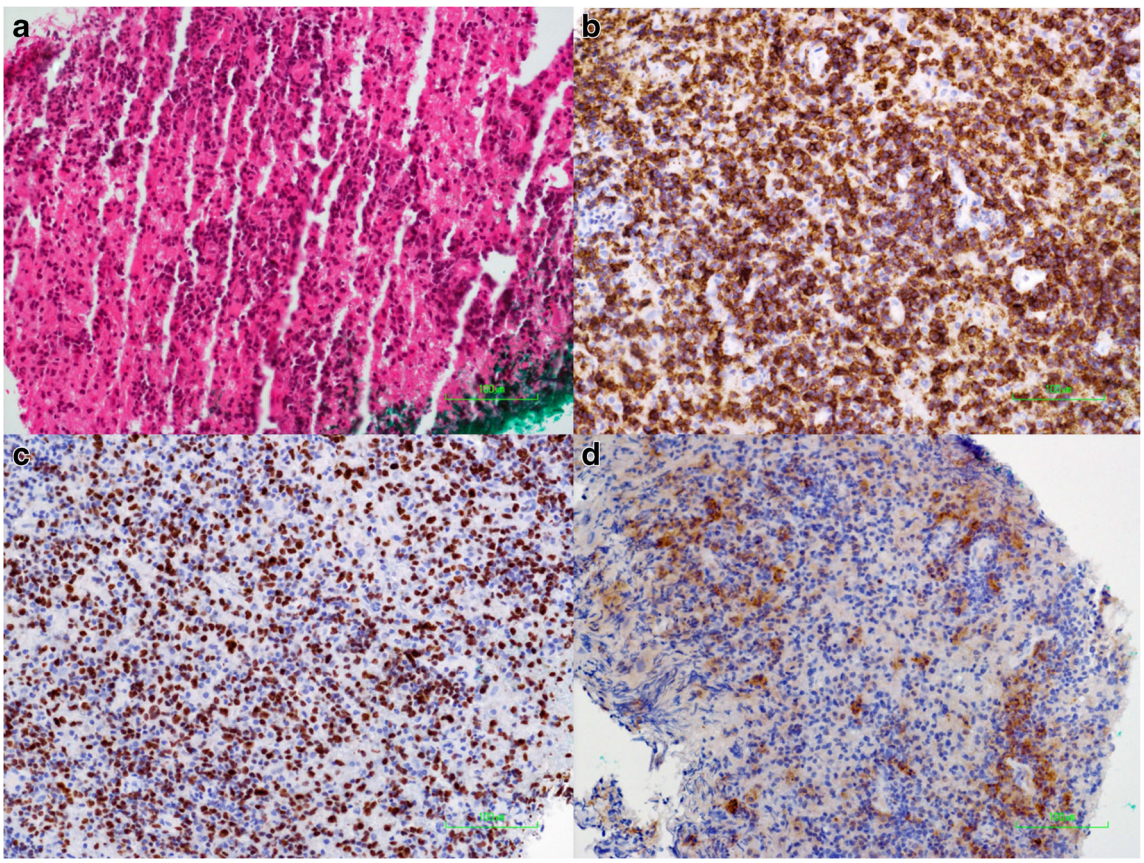

Fig. 2 Histology of the left frontal lobe lesion. **a** Clusters of large neoplastic lymphoid cells were seen in the brain parenchyma with angiocentric growth pattern (hematoxylin eosin, original magnification × 200). **b** Lymphoma cells were almost 100% positive for CD20 (immunoperioxidase, original magnification × 200). **c** About 70% of lymphoma cells stained positive for the proliferation marker Ki-67 (immunoperoxidase, original magnification × 200). **d** Approximately 10% of lymphoma cells showed PD-L1 expression (immunoperoxidase, original magnification × 200)

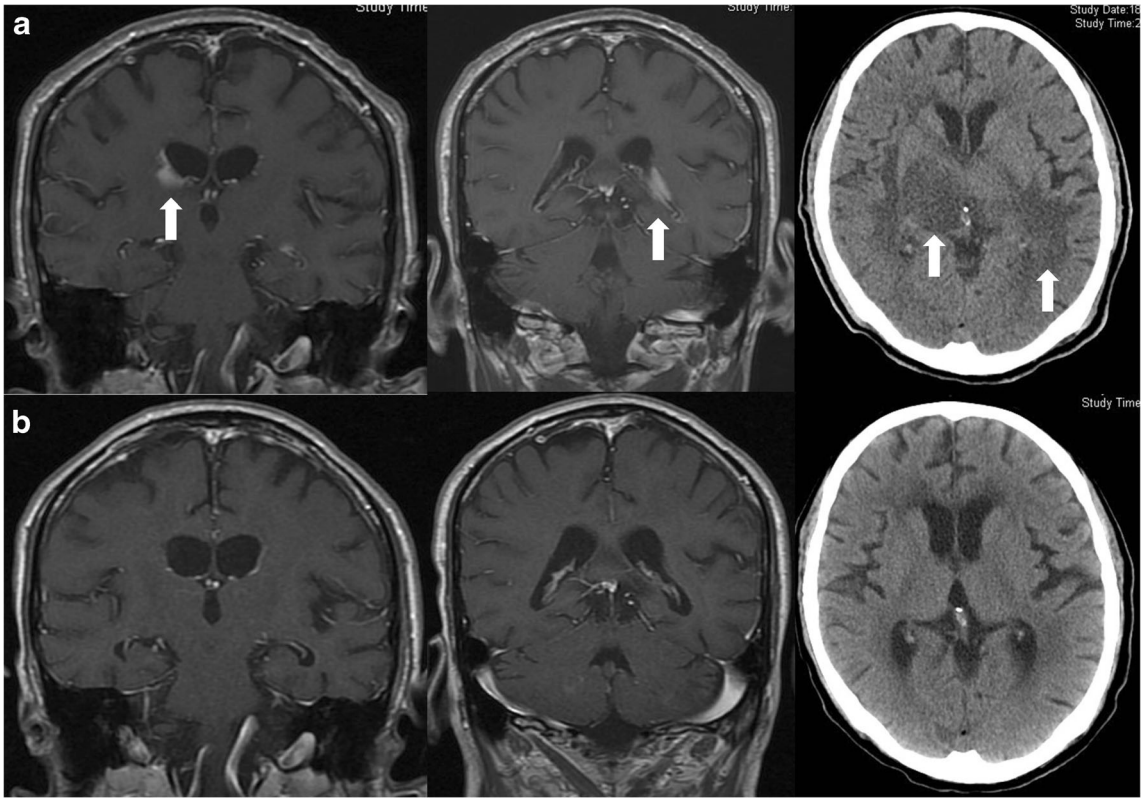

Fig. 3 Responses to low-dose nivolumab therapy. **a** Lesions at relapse. Post-contrast coronal magnetic resonance imaging (MRI) showing involvement of periventricular white matter adjacent to right lateral ventricle (arrow, left panel) and left occipital horn (arrow, middle panel). Computed tomography (CT) scan performed four weeks later showing disease progression with extensive infiltration with associated vasogenic edema in the basal ganglia (arrows, right panel). **b** Resolution of lesions after nivolumab treatment. Post-contrast coronal MRI corresponding to those in **a** (left and middle panels) showing resolution of lesions after four doses of nivolumab. CT scan corresponding to the section in **a** (right panel) showing resolution of lesions after two doses of nivolumab

(3 mg/kg Q2W) had previously been reported in four cases of relapsed/refractory PCNSL [6], with three patients achieving CR. However, two patients ultimately relapsed at 14 and 17 months. The first patient relapsed systemically, challenging the diagnosis of PCNSL, where extracranial spread should be rare. The second patient had nivolumab treatment truncated after three cycles because of end-stage renal failure requiring hemodialysis. Only the third patient had on-going response 13 months after treatment. Our patient was therefore just the second case to date of PCNSL achieving durable CR with nivolumab, having a progression-free survival of 24+ months.

Another interesting finding was the swift response. Our patient improved clinically after the first dose, and dramatic radiologic improvement occurred after the second dose. This was consistent with previous observations [6], with the median cycles of nivolumab leading to an objective response being 3 (range, 2–4).

More impressive was the dose of nivolumab administered. We used nivolumab at 40 mg (the smallest vial available) Q2W, much lower than 3 mg/kg Q2W previously reported in PCNSL [6], and 240 mg Q2W currently approved for lymphomas and other solid tumors. We used low-dose nivolumab based on our previous observations of the efficacy of 40 mg Q2W in Hodgkin lymphoma [7], acute lymphoblastic leukemia relapse after allogeneic HSCT [8], and NK/T cell lymphoma [9, 10]. Herein, we showed again that nivolumab at 40 mg Q2W was effective for PCNSL. It is truly remarkable that merely 80 mg of nivolumab was already enough to induce excellent clinical and radiologic responses in this patient, who had failed high-dose cytarabine and methotrexate, and WBRT.

With the low-dose regimen, the cumulative dose in two years only amounted to about 7 cycles of nivolumab at the approved dosage of 240 mg Q2W. Our strategy ensured prolonged PD1 blockade while minimizing irAE [9, 10] and economizing on drug cost. These aspects are particularly meaningful for prolonged PD1 blockade, which might be conducive to maintaining the response.

In conclusion, we showed that nivolumab was highly effective for relapsed PCNSL. Nivolumab should arguably be tried initially in relapsed/refractory PCNSL, because clinical benefits are swift. If a response is not observed with the initial several courses, precious time would still not be lost for other salvage approaches. Finally, low-dose nivolumab is efficacious, economic, and may decrease irAEs.

Author contribution T.S.Y. Chan: treated the patient and wrote and approved the manuscript

P.L. Khong: performed the radiodiagnostics and wrote and approved the manuscript

R. Au-Yeung: performed the histopathologic diagnosis and wrote and approved the manuscript

Y.L. Kwong: treated the patient and wrote and approved the manuscript

E. Tse: treated the patient and wrote and approved the manuscript

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Patient gave informed consent to treatment.

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