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Letter to the Editor

Cerebrospinal fluid lymphocytosis: a hallmark of neurological complications during checkpoint inhibition

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To the Editor,

Outcomes of several cancer types have improved significantly with the introduction of immune checkpoint inhibitors (ICIs), targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; ipilimumab) or programmed cell death-1 (PD-1) receptors (e.g. pembrolizumab and nivolumab) on T cells to induce antitumour immune responses [1]. A variety of immune-related toxicities is observed with ICI use that can affect any organ in the body [2].

Although rare and difficult to diagnose owing to their heterogeneous presentation, neurological ICI toxicity causes significant morbidity and mortality [3]. Reviewing 31059 cases, Wang et al [4] reported 613 fatal cases of ICI toxicity; of which, 193 were related to anti–CTLA-4 monotherapy, 333 to anti–PD-1 or anti–PD-L1 and 87 to combined ICI therapy. Fatal toxicities were of neurologic origin in 11 (6%), 50 (15%) and 7 (8%) cases [4]. These fatal events underline the need for early recognition and initiating treatment as soon as possible.

Here, we report 7 consecutive cases of severe (Common Toxicity Criteria $\geq$ grade 3) neurotoxicity in 323 ICI-treated patients at our institute between January 2015 and November 2018. All patients displayed marked cerebrospinal fluid (CSF) lymphocytosis ($>3 \times 10^6$ leukocytes per litre with $\geq$70–99% lymphocytes). In our view, CSF lymphocytosis is a potential diagnostic aid and should be included in the diagnostic work-up in case of suspected ICI neurotoxicity.

Patient characteristics, presenting symptoms, CSF findings, immunosuppressive treatment and response are summarised in Table 1. All patients received PD-1 inhibition, in three cases combined with CTLA-4 inhibition. One patient received vemurafenib treatment after 1 cycle of ICI therapy. Five patients were treated for metastatic melanoma, one for stage IV non–small-cell lung cancer and one for stage IV renal cell carcinoma. Symptoms at presentation were fever (4/7), headache (4/7), dysarthria (1/7), muscle weakness (1/7), neck stiffness (1/7), faecal incontinence (1/7), nausea with vomiting (1/7), facial nerve palsy (1/7) and an altered mental state, such as

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Table 1
Patient characteristics, presenting symptoms and diagnostics.

Case no.	Gender (age)	ICI (no. of cycles)	Malignancy	Time to onset in days	Leukocytes/L in CSF % of lymphocytes	Clinical diagnosis	Immunosuppressive treatment	Resolution of symptoms
1	M (68 y)	Nivolumab (9)	Renal cell carcinoma	214	14×10^6 70%	Encephalitis	Dexamethasone 40 mg/day + IVIG	Partial
2	M (65 y)	Pembrolizumab (1)	Melanoma	46	82×10^6 88%	Radiculitis	Prednisolone 2 mg/kg + IVIG	Partial
3	M (57 y)	Ipilimumab (4) > nivolumab (1)	Melanoma	92	59×10^6 99%	Meningitis	Methylprednisolone 1.5 mg/kg	Complete
4	F (58 y)	Ipilimumab (4) > nivolumab (2)	Melanoma	21	18×10^6 92%	Encephalitis	Dexamethasone 200 mg + IVIG	Complete
5	F (38 y)	Ipilimumab + nivolumab (2)	Melanoma	24	152×10^6 92%	Aseptic meningitis	Prednisolone 2 mg/kg	Complete
6	M (69 y)	Nivolumab (2)	Non–small-cell lung cancer	34	$33 * 10^6$ 88%	Encephalitis	Prednisolone 1 mg/kg	Partial
7	M (55 y)	Ipilimumab + nivolumab (2)	Melanoma	32	21×10^6 93%	Aseptic meningitis/neuritis	Prednisolone 2 mg/kg	Complete

no. = number; y = years; IVIG = intravenous immunoglobulin; L = litre; CSF = cerebrospinal fluid.
IVIGs, 400 mg/kg/day for 5 days.

cognitive impairment and confusion (3/7). The median time from start of checkpoint inhibition to the onset of symptoms was 34 days (range: 22–214). Clinical diagnosis was aseptic meningitis in three patients, encephalitis in three patients and radiculitis in one patient.

In all cases, there was marked lymphocytosis (70–99%) of the CSF. Alternative diagnoses such as intracranial haemorrhage or stroke, brain or leptomeningeal metastases and infectious causes were ruled out with appropriate diagnostic tests including magnetic resonance imaging and CSF cytology, polymerase chain reaction and cultures. All patients were treated with high-dose steroids as indicated in Table 1. Subsequent intravenous immunoglobulins were administered in three patients. All patients experienced neurological improvement after immunosuppressive treatment within three days, with complete resolution of symptoms in four patients. Immune checkpoint inhibition was not reintroduced after neurological toxicity in any of the patients. Four patients died of progressive disease 1–6 months after presentation of neurological symptoms. Two patients died of other causes (cerebral bleeding and myocardial infarction), 3 months and 7 months later, respectively. One patient with metastatic melanoma (case 5) has been experiencing an ongoing response to ICI, now 2 years after treatment initiation.

Discussion

We found CSF lymphocytosis in all 7 patients who presented with severe neurotoxicity during ICI therapy in our institute, despite distinct symptomatology and diagnosis. Although CSF lymphocytosis has been reported in a few cases of encephalitis and/or meningitis [3,5], CSF leucocyte counts are not regularly assessed in patients experiencing neurological symptoms during ICI therapy. Moreover, although current guidelines recommend CSF analysis in the diagnostic work-up of neurotoxicity [2,6], lymphocytic pleocytosis has not been recognised as a hallmark of ICI neurotoxicity thus far. The presence of CSF lymphocytosis in all patients presenting with severe ICI neurotoxicity strongly suggests that it can be a diagnostic clue for this challenging diagnosis. Neurotoxicity during ICI therapy caused significant burden for the patients described, although rapid clinical recovery was observed on initiation of immunosuppressive treatment in most cases. We suggest that prompt initiation of steroid treatment for CSF lymphocytosis could potentially decrease the morbidity and mortality of ICI neurotoxicity.

The neurological toxicity that was observed after treatment switch to BRAF inhibition in the second patient was considered immune related as symptoms emerged after treatment switch are not known as vemurafenib toxicity and resolved under immunosuppressive treatment (while vemurafenib was continued). Luxation of ICI toxicity by BRAF inhibitor treatment has been described previously [7], potentially driven by the upregulation of Major Histocompatibility Complex Class I (MHC-I) expression upon Mitogen-Activated Protein Kinase (MAPK) pathway inhibition [8].

Our data illustrate that CSF lymphocytosis can be used as a diagnostic aid for the challenging diagnosis of neurological ICI toxicity. As CSF lymphocytosis is not pathognomonic for ICI neurotoxicity, alternative diagnoses, such as viral infections, should always be ruled out. We encourage clinicians to assess CSF leucocyte differentiation and initiate immunosuppressive treatment when lymphocytosis is found in patients with neurological symptoms during ICI therapy without an alternative explanation.

Conflict of interest statement

T.E.H.J. and S.T.J. declare no conflicts of interest. K.J.J. holds a consulting/advisory relationship (paid to institution) with Novartis. L.A.S.R. holds a consulting/advisory relationship with and received honoraria from (paid to institution) Roche and AstraZeneca. S.K.P.M. holds a consulting/advisory relationship with and received honoraria (paid to institution) from Bristol-Myers Squibb, MSD, Novartis, Roche and Pierre Fabre.

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