

## Immune checkpoint inhibitor therapy-associated encephalitis: a case series and review of the literature

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### Summary

**BACKGROUND:** Immune checkpoint inhibitors (ICIs) can cause a wide spectrum of immune-related adverse events, including encephalitis. To date, no prospective randomised controlled trials examining the patient characteristics, treatment and outcomes of ICI-associated encephalitis have been published. Therefore, we aimed to review case reports and to provide recommendations for the management of ICI-associated encephalitis.

**METHODS:** A literature search using Google Scholar and PubMed was performed in December 2019. Published case reports and case series of ICI-associated encephalitis were reviewed, and a case series from the Limmattal Hospital in Schlieren, Switzerland was added. The results are presented as numbers and medians (ranges).

**RESULTS:** Five different ICIs caused encephalitis in the 47 patients included in this case series. Nivolumab was the most frequently involved drug (27/47, 57%). The median time between treatment and onset of symptoms was 65 (4–630) days. Patients presented with rapidly evolving confusion, reduced level of consciousness, headache, seizures and focal neurological deficits. A total of 19 out of the 44 (43%) magnetic resonance imaging (MRI) scans performed revealed findings suggestive of encephalitis. No specific electroencephalogram (EEG) pattern consistent with encephalitis was found, but epileptiform discharges were detected in 7/20 (35%) of all tested patients. Typical findings of cerebrospinal fluid (CSF) analysis were pleocytosis, elevated protein levels and normal glucose concentrations. Forty-four out of 47 (94%) patients received corticosteroids. Intravenous immunoglobulins (IVIG), rituximab and plasma exchange therapy were less frequently prescribed. Nine out of 47 (19%) patients died during the index hospitalisation.

**CONCLUSIONS:** Encephalitis should be suspected in patients treated with ICIs who present with rapidly evolving confusion. Blood tests, CSF analysis, cerebral MRI and an

EEG should be performed. Therapy with intravenous corticosteroids is recommended. Steroid unresponsiveness is rare and should lead to a review of the diagnosis. Alternative treatment options are IVIG, plasma exchange therapy and rituximab.

**Keywords:** immune checkpoint inhibitor, nivolumab, pembrolizumab, ipilimumab, encephalitis

### Introduction

Immune checkpoint inhibitors (ICIs) re-establish the anti-tumour activity of T-lymphocytes by blocking immune inhibitory receptors such as programmed cell death protein 1 (PD-1, e.g., nivolumab, pembrolizumab and lambrolizumab), programmed cell death ligand 1 (e.g., atezolizumab, durvalumab and avelumab) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4, e.g., ipilimumab) [1–3]. They are effective in patients with melanoma, lung cancer, renal cell cancer, urothelial cancer and other tumour types [4–6].

ICIs have been associated with various neurological immune-related adverse events, including peripheral neuropathies, Guillain-Barré syndrome, myasthenia gravis, Tolosa-Hunt syndrome and autoimmune encephalitis. According to the literature, less than 1% of patients will develop autoimmune encephalitis when treated with ICIs [4, 6, 7], with higher risks during concurrent or sequential ICI use [6].

In the absence of prospective randomised controlled trials examining the patient characteristics, treatment and outcomes of ICI-associated encephalitis, we reviewed the published case reports of ICI-associated encephalitis and added our own five cases. Recommendations for the management of ICI-associated encephalitis are presented.

### Methods

A literature search using Google Scholar and PubMed and focusing on publications in English was performed in December 2019. The following search terms were used: “im-

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mune checkpoint inhibitors”, “checkpoint inhibitor therapy”, “checkpoint inhibitor treatment”, “ipilimumab”, “pembrolizumab”, “atezolizumab”, “nivolumab”, “durvalumab”, “avelumab”, “encephalitis”, “encephalopathy”, “case report” and “case series”. Additionally, the bibliographies of the retrieved publications were screened. The patient characteristics, treatments and outcome parameters were entered into a Microsoft Excel® (2011) worksheet.

#### ABBREVIATIONS

<b>ANCA</b>	anti-neutrophil cytoplasmic antibody
<b>AGNA</b>	anti-glia nuclear antibody, SOX1
<b>Anti-AchR antibody</b>	anti-acetylcholine receptor antibody
<b>Anti-AMPA 1 antibody</b>	anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor 1 antibody
<b>Anti-AMPA 2 antibody</b>	anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor 2 antibody
<b>Anti-CASPR2 antibody</b>	anti-contactin-associated protein-like 2 antibody
<b>Anti-CRMP5 antibody</b>	anti-collapsin response mediator protein 5 antibody, CV2
<b>Anti-DPPX antibody</b>	anti-dipeptidyl-peptidase-like protein 6 antibody
<b>Anti-GABAR antibody</b>	anti-gamma aminobutyric acid B receptor antibody
<b>Anti-GAD65 antibody</b>	anti-glutamate decarboxylase 65 kDa isoform antibody
<b>Anti-Gly antibody</b>	anti-glycine antibody
<b>Anti-Hu antibody</b>	anti-neuronal nuclear antibody-1, ANNA1
<b>Anti-LG1 antibody</b>	anti-leucine-rich glioma-inactivated 1 antibody
<b>Anti-NMDAR antibody</b>	anti-N-methyl-D-aspartate receptor antibody
<b>Anti-Ri antibody</b>	anti-neuronal nuclear antibody-2, ANNA2
<b>Anti-TG antibody</b>	anti-thyroglobulin antibody
<b>Anti-TPO antibody</b>	anti-thyroid peroxidase antibody
<b>Anti-TR antibody</b>	anti-human thrombin receptor antibody
<b>Anti-Yo antibody</b>	anti-Purkinje cell cytoplasmic antibody type 1, PCA-1
<b>Anti-VGKC antibody</b>	anti-voltage-gated potassium channel antibody
<b>Anti-VGCC antibody</b>	anti-voltage-gated calcium channel antibody
<b>Anti-ZIC4 antibody</b>	anti-zic family member 4 antibody
<b>EEG</b>	electroencephalogram
<b>CSF</b>	cerebrospinal fluid
<b>CTLA-4</b>	cytotoxic T-lymphocyte-associated antigen 4
<b>FLAIR</b>	fluid-attenuated inversion recovery
<b>HSV-1</b>	herpes simplex virus type 1
<b>HSV-2</b>	herpes simplex virus type 2
<b>ICI</b>	immune checkpoint inhibitor
<b>ICU</b>	intensive care unit
<b>IV</b>	intravenous
<b>IVIG</b>	intravenous immunoglobulins
<b>MRI</b>	magnetic resonance imaging
<b>NAEs</b>	neurological adverse events
<b>NSCLC</b>	non-small cell lung cancer
<b>PCR</b>	polymerase chain reaction
<b>PD-1</b>	programmed cell death protein 1
<b>PRES</b>	posterior reversible encephalopathy syndrome
<b>SCLC</b>	small cell lung cancer
<b>VZV</b>	varicella zoster virus

Five patients with ICI-associated encephalitis treated at the Limmattal Hospital in Schlieren, Switzerland were added to this case series. Written consent was obtained from the patients or their next of kin. Data were collected from electronic medical records.

## Results

Five cases of ICI-associated encephalitis were diagnosed in the Limmattal Hospital in Schlieren, Switzerland from 2016 to 2020. One case was previously described by Schneider et al. [6]. Detailed descriptions of the four remaining patients are provided in appendix 1. All five patients were included in the case series. The literature search identified 29 published cases. A bibliography screening revealed 13 additional publications. Overall, 47 cases were analysed.

Five different ICIs were implicated in the pathogenesis of autoimmune encephalitis, either as monotherapy or as concurrent or sequential combination therapy. These five drugs were atezolizumab (n = 4), ipilimumab (n = 14), lambrolizumab (n = 1), nivolumab (n = 27) and pembrolizumab (n = 10). No incidences of avelumab- or durvalumab-associated encephalitis were reported. The median (range) delay between the start of ICI treatment and the onset of symptoms was 65 (4–630) days.

The median (range) patient age was 63 (18–83) years. Patients presented with reduced levels of consciousness, confusion, headache, fever, seizures and/or focal neurological deficits (e.g., motor deficits, paraesthesia, aphasia or ataxia). Other symptoms or signs included asterixis, myoclonus, memory loss, nausea, vomiting and abnormal behaviours (e.g., inappropriate laughter). The patient characteristics are summarised in table 1.

Cerebral magnetic resonance imaging (MRI) was performed in 44/47 (94%) patients. In 25/44 (57%) patients, cerebral MRI was normal or showed nonspecific abnormalities. In 19/44 (43%) patients, cerebral MRI findings were consistent with encephalitis. These findings included leptomeningeal enhancement, bilateral hyperintensities in the mesial temporal area or in the basal ganglia, and diffuse encephalitis resembling disseminated demyelination.

An electroencephalogram (EEG) was obtained in 20/47 (43%) patients. No specific EEG pattern was found. Epileptic activity was recorded in 7/20 (35%) patients. The findings of the cerebral MRIs and EEGs are summarised in table 2.

Cerebrospinal fluid (CSF) was analysed in 37/47 (79%) patients. Pleocytosis was found in 30/37 (81%) patients. An increased leucocyte count was found in 24/37 (65%) patients, of whom 16/37 (43%) had lymphocytosis, 2/37 (5%) had monocytosis and 1/37 (3%) had an increased proportion of neutrophils. In 5/37 (14%) patients, the leukocytes were not further differentiated. Protein levels were increased in 24/32 patients (75%, 270 to >6,000 mg/l), but glucose levels were normal in the majority of patients (19/24 patients, 79%). The detailed results of the CSF analyses are provided in table 3.

One or more antibodies could be detected in 13/25 (52%) patients. The following antibodies were found: anti-CASPR2 (n = 1), anti-GAD65 (n = 2), AGNA (n = 1), anti-Hu (n = 3), anti-NMDAR (n = 2), anti-Ma2 (n = 2),

Table 1: Patient characteristics.

Case report	Year of publication	Country	Age	Sex	Cancer type	Brain metastases	Cancer therapy	Steroid dose <sup>†</sup>	Hospital survival
<b>Limmattal Hospital</b>									
See appendix 1	n/a	CH	74	F	Pulmonary adenocarcinoma	No	Pembrolizumab	125	Yes
See appendix 1	n/a	CH	58	F	Carcinosarcoma of the uterus	Yes	Pembrolizumab	80	No
See appendix 1	n/a	CH	63	F	Pulmonary adenocarcinoma	No	Nivolumab	125	Yes
Schneider et al. [6]	2017	CH	78	M	Pulmonary squamous cell carcinoma	No <sup>†</sup>	Nivolumab	80	Yes
See appendix 1	n/a	CH	79	M	Merkel cell carcinoma	Yes	Nivolumab + Ipilimumab	125	Yes
<b>Literature search</b>									
Larkin et al. [4]	2017	USA	53	F	Malignant melanoma	No	Nivolumab + Ipilimumab	200	Yes
Larkin et al. [4]	2017	USA	61	M	Malignant melanoma	No	Nivolumab + Ipilimumab → Nivolumab alone	1000	Yes
Larkin et al. [4]	2017	USA	57	M	Malignant melanoma	No	Nivolumab → Ipilimumab → Nivolumab	n.r.	Yes
Larkin et al. [4]	2017	USA	83	M	Malignant melanoma	No	Nivolumab	24	No
Larkin et al. [4]	2017	USA	58	F	Malignant melanoma	Yes	Nivolumab	1000	Yes
Shah et al. [8]	2018	USA	66	F	Pulmonary adenocarcinoma	No	Nivolumab	1000	No
Shah et al. [8]	2018	USA	44	F	Pulmonary adenocarcinoma	Yes	Nivolumab	1000	Yes
Williams et al. [9]	2016	USA	55	F	Malignant melanoma	Yes	Nivolumab + Ipilimumab	1000	Yes
Williams et al. [9]	2016	USA	65	M	Small cell lung cancer	Yes	Nivolumab + Ipilimumab	48	Yes
Niki et al. [10]	2016	Japan	51	M	Pulmonary squamous cell carcinoma	Yes	Pembrolizumab	2 mg/kg	Yes
Cook et al. [11]	2017	USA	72	M	Malignant melanoma	Yes	Pembrolizumab	High dose	No
Kim et al. [12]	2019	Korea	49	M	Urothelial carcinoma of the bladder	n.r.	Atezolizumab	1000	Yes
Mandel et al. [13]	2014	USA	66	M	Malignant melanoma	No	Lambrolizumab	None	Yes
Laserna et al. [14]	2018	USA	53	F	Cervical squamous cell carcinoma	No	Atezolizumab	90	Yes
Levine et al. [15]	2017	USA	59	F	Urothelial carcinoma of the bladder	Yes	Atezolizumab	200	Yes
Bossart et al. [7]	2017	CH	60	F	Malignant melanoma	Yes	Ipilimumab + Pembrolizumab	None	No
Arakawa et al. [16]	2019	Japan	78	M	Pulmonary adenocarcinoma	n.r.	Atezolizumab	1000	Yes
Salam et al. [17]	2016	UK	64	M	Malignant melanoma	No	Pembrolizumab	High dose	Yes
Ito et al. [18]	2017	Japan	75	M	Small cell lung cancer	Yes	Nivolumab + Ipilimumab	500	Yes
Conry et al. [19]	2015	USA	41	M	Malignant melanoma	No	Ipilimumab	160	Yes
Burke et al. [20]	2018	USA	64	F	Ovarian clear cell carcinoma	No	Nivolumab	12,000	Yes
Boyd et al. [21]	2015	UK	71	M	Malignant melanoma	No	Ipilimumab	1000	Yes
Voskens et al. [22]	2013	DE	50	M	Malignant melanoma	No	Ipilimumab	High dose	Yes
Cao et al. [23]	2016	USA	76	F	Malignant melanoma	Yes	Ipilimumab	High dose	Yes
Khoja et al. [24]	2016	Canada	51	F	Malignant melanoma	No	Pembrolizumab	1000	Yes
Kazandjian et al. [25]	2016	USA	70	F	Non-small cell lung cancer	n.r.	Nivolumab	2–4 mg/g	No
Carl et al. [26]	2015	DE	64	M	Prostate cancer	No	Ipilimumab	1000	Yes
Richard et al. [27]	2017	USA	74	M	Pulmonary squamous cell carcinoma	Yes	Nivolumab	n.r.	Yes
Matsuo et al. [28]	2018	Japan	60	M	Pulmonary pleomorphic carcinoma	n.r.	Nivolumab	High dose	No
Brown et al. [1]	2017	Australia	67	M	Malignant melanoma	n.r.	Pembrolizumab	High dose	Yes
Feng et al. [29]	2017	Australia	66	M	Pulmonary adenocarcinoma	Yes	Pembrolizumab	1000	Yes
Strik et al. [30]	2017	DE	53	M	Non-Hodgkin lymphoma	No	Nivolumab	1000	Yes
Chaucer et al. [31]	2018	USA	44	M	Renal cell carcinoma	No	Nivolumab	n.r.	Yes

Case report	Year of publication	Country	Age	Sex	Cancer type	Brain metastases	Cancer therapy	Steroid dose <sup>†</sup>	Hospital survival
Leitinger et al. [32]	2018	Austria	67	F	Pulmonary squamous cell carcinoma	n.r.	Nivolumab	1000	No
Zurko et al. [33]	2018	USA	20	M	Hodgkin lymphoma	No	Nivolumab	160	Yes
Kopecký et al. [34]	2018	Czech Republic	63	M	Renal cell carcinoma	No	Nivolumab	2 mg/kg	Yes
De la Hoz et al. [35]	2018	USA	28	F	Hodgkin lymphoma	n.r.	Nivolumab	1 mg/kg	Yes
Shibaki et al. [36]	2019	Japan	78	M	Malignant pleural mesothelioma	No	Nivolumab	n.r.	Yes
Zafar et al. [37]	2019	USA	59	F	Laryngeal squamous cell carcinoma	n.r.	Nivolumab	1000	Yes
Gill et al. [38]	2019	USA	68	F	Merkel cell carcinoma	No	Nivolumab	1000	No
Hottinger et al. [39]	2018	CH	71	F	Small cell lung cancer	n.r.	Nivolumab + Ipilimumab	1000	Yes
Gill et al. [38]	2019	USA	71	F	Pulmonary adenocarcinoma	n.r.	Pembrolizumab	n.r.	Yes

F = female; M = male; n/a = not applicable; n.r. = not reported \* Daily methylprednisolone dose or equivalent (mg) † Intracranial epidermoid with R2 resection previously

anti-Ri (n = 1), an uncharacterised antibody against Purkinje cells (n = 1) and an unclassified antibody (n = 1). One patient with steroid-responsive encephalopathy associated with autoimmune thyroiditis presented with anti-TPO and anti-TG antibodies. In 12/25 patients (48%), testing for antibodies was negative.

Brain metastases were present in 14/47 (30%) patients. Antibiotics and/or antiviral therapy were initially prescribed in 16/47 (34%) patients. Intravenous treatment with corticosteroids was started in 44/47 (94%) patients. Typically, “high” (>30 mg) and “very high” (>100 mg) daily corticosteroid doses were used [40]. The mean (range) dose was 997 (24–12,000) mg methylprednisolone or equivalent per day. Usually, the intravenous regimen was changed to oral administration after five days and then tapered over several weeks. In 6/47 patients (13%) the corticosteroid dose was simply specified as “high-dose”; in another 4/47 patients (9%), the dose was not specified at all. In addition, twelve patients (26%) received intravenous immunoglobulins (IVIG), six patients (12%) were given rituximab, and four patients (9%) underwent plasma exchange therapy.

Nine out of 47 (19%) patients died during hospitalisation, of whom six patients received a mean (range) corticosteroid dose of 541 (24–1000) mg, two patients received “high-dose” corticosteroids (not further specified), and the remaining patient received no corticosteroid therapy at all.

## Discussion

In this study, we analysed five patients treated in our hospital and combined these findings with those of 42 patients described in published case reports and case series. Based on these findings, we provide recommendations for the management of ICI-associated encephalitis.

The ICIs nivolumab, ipilimumab, pembrolizumab, atezolizumab and lambrolizumab were involved in the pathophysiology of ICI-associated encephalitis. Less than half of the MRIs performed revealed findings suggestive of encephalitis. No specific EEG pattern consistent with encephalitis was found, but epileptiform discharges were detected in approximately one third of the EEGs. The majority of patients had CSF pleocytosis, elevated CSF protein levels and normal CSF glucose concentrations. The patients usually received therapy with corticosteroids, where-

as IVIG, rituximab and plasma exchanges were less frequently administered.

## Risk factors

In general, CTLA-4 inhibitors (e.g., ipilimumab) are associated with a higher incidence of immune-related adverse events than PD-1 inhibitors (e.g., nivolumab, pembrolizumab and lambrolizumab). When two ICIs (e.g., nivolumab + ipilimumab or pembrolizumab + ipilimumab) are given concurrently, the risk seems to be even higher [41–43]. In our review, 29/47 cases (62%) were caused by PD-1 inhibitor monotherapy, and 5/47 cases (11%) were caused by CTLA-4 inhibitor monotherapy. The concurrent or sequential use of ICIs caused encephalitis in 9/47 cases (19%).

Paraneoplastic antibodies (e.g., anti-Hu, anti-Yo, anti-Ma2, anti-CRMP5, anti-amphiphysin, anti-Ri, anti-NMDA, anti-VGKC, anti-VGCC and anti-AChR) can develop in tumour patients and are associated with various neurological diseases [44]. The presence of paraneoplastic antibodies may increase the risk of developing ICI-associated encephalitis [38].

In our case series, one or more antibodies could be detected in 52% of the patients tested (anti-CASPR2, anti-GAD65, anti-AGNA, anti-Hu, anti-NMDAR, anti-Ma2, anti-Ri and anti-TPO/TG). Shah et al. [8] reported a patient with pulmonary adenocarcinoma and type 1 diabetes who developed GAD65 antibody-positive encephalitis after treatment with nivolumab. GAD65 is located on pancreatic islet cells as well as on GABAergic neurons of the central nervous system. This patient had a higher risk for ICI-associated encephalitis, as he presumably had pre-existing GAD65 antibodies in association with his diabetes.

## Presentation and diagnosis

In our experience, ICI-associated encephalitis should be suspected in patients with rapidly evolving confusion. Other symptoms associated with immune-mediated encephalitis include reduced level of consciousness, headache, seizures and focal neurological deficits. One third of patients presented with fever. The time interval between the start of immune checkpoint blockade and the onset of symptoms was wide, ranging from less than a week to 21 months, with a median of 9 weeks. In the case series of

Table 2: MRI and EEG findings.

Case report	Year of Publication	Brain MRI	EEG
<b>Limmattal Hospital</b>			
See appendix 1	n/a	No signs of encephalitis or meningitis.	Moderate background slowing, focal slowing over the right temporal region, some epileptiform activity with bilateral frontal sharp waves.
See appendix 1	n/a	25 × 24 mm metastatic lesion subcortically located in the left medial frontal gyrus. Otherwise, normal MRI.	n.r.
See appendix 1	n/a	Diffuse white matter changes, most likely due to whole brain radiation.	n.r.
Schneider et al. [6]	2017	No signs of encephalitis, carcinomatous meningitis, metastases or stroke.	Moderate background slowing and focal delta slowing over the left temporal region with singular sharp waves in this region.
See appendix 1	n/a	No signs of encephalitis, hypophysitis or ischaemia.	Mild background slowing, moderate focal slowing over the left temporal region. No epileptiform activity.
<b>Literature search</b>			
Larkin et al. [4]	2017	No signs of metastasis or stroke.	Diffuse, marked cerebral slowing.
Larkin et al. [4]	2017	Abnormally high fluid-attenuated inversion recovery (FLAIR) signal without evidence of brain metastasis.	Epileptic activity.
Larkin et al. [4]	2017	No signs of brain metastasis.	Diffuse slowing and triphasic waves and phase reversal in the right frontal region. No sign of seizure activity.
Larkin et al. [4]	2017	Some areas of hypersignal on the supratentorial white matter and FLAIR without a break in the haematocephalic barrier, probably caused by microangiopathy.	n.r.
Larkin et al. [4]	2017	No signs of stroke, brain metastases unchanged, no new lesions.	n.r.
Shah et al. [8]	2018	Symmetric T2 hyperintense and T1 hypointense basal ganglia abnormalities. A repeat brain MRI three weeks later re-demonstrated symmetric T2 hyperintense basal ganglia but with a transition to T1 hyperintensities in the same location.	n.r.
Shah et al. [8]	2018	T2 signal hyperintensities of the bilateral mesial temporal lobes compatible with limbic encephalitis. Additionally, there were two enhancing foci within the left occipital and right temporal lobes, concerning for metastatic disease.	n.r.
Williams et al. [9]	2016	Stable encephalomalacia at sites of prior radiosurgery with no additional metastases. No changes were noted at previously irradiated tumour sites.	Serial EEG showed intermittent bilateral slowing, then a sub-clinical seizure of left temporo-occipital origin. Continuous EEG monitoring showed intermittent periods of rhythmic epileptiform activity in the left temporal lobe without clinical correlations.
Williams et al. [9]	2016	New nonspecific T2 hyperintensities in the right mesial temporal lobe.	n.r.
Niki et al. [10]	2016	No abnormality other than the previous surgical resection.	Slow wave in the right frontal lobe, which indicated encephalitis or the aftermath of the previous brain metastasis.
Cook et al. [11]	2017	Restricted diffusion in the basal ganglia and right temporal lobe.	n.r.
Kim et al. [12]	2019	Diffuse leptomeningeal enhancement.	Status epilepticus.
Mandel et al. [13]	2014	Unremarkable but limited due to motion artefact. A follow-up brain MRI scan showed stable T2 FLAIR hyperintensities in the right frontal and left occipital lobes, with improvement in the signal originating from both external capsules.	Periodic epileptiform discharges.
Laserna et al. [14]	2018	Diffuse leptomeningeal enhancement.	No acute abnormalities. The EEG was repeated and showed non-convulsive status epilepticus.
Levine et al. [15]	2017	1.0 × 0.9 cm mildly enhancing lesion in the left frontal lobe with no vasogenic oedema or mass effect.	n.r.
Bossart et al. [7]	2017	n.r.	n.r.
Arakawa et al. [16]	2019	No abnormal findings other than the left temporal lobectomy.	n.r.
Salam et al. [17]	2016	Bilateral symmetrical T2 signal change with atrophy within the hippocampi, extending into the anterior temporal lobe and insula. This was more extensive on the left side, with significant volume loss. Previous MRI performed at the referring hospital in November 2014 was reviewed and showed a bilateral high T2 signal affecting the limbic structures, again predominantly on the left, though without volume loss.	No epileptic activity.
Ito et al. [18]	2017	No recurrence of brain metastasis, haemorrhage or infarction.	No epileptic activity.
Conry et al. [19]	2015	New area of restricted diffusion in the posterior splenium of the corpus callosum, with corresponding T2 hyperintensity on FLAIR and no abnormal enhancement or evidence of melanoma metastasis.	n.r.
Burke et al. [20]	2018	No signs of encephalitis or metastasis.	n.r.
Boyd et al. [21]	2015	Unchanged.	n.r.

Case report	Year of Publication	Brain MRI	EEG
Voskens et al. [22]	2013	Enhancement in both trigeminal nerves and, additionally, three parenchymal lesions with no indication of meningeosis carcinomatosa or pituitary enlargement.	n.r.
Cao et al. [23]	2016	New signal abnormalities in the left optic nerve, left inferior frontal lobe, and splenium of the corpus callosum, which extended into the parietal lobe and bordered on the stereotactic radiosurgery-treated lesion that by now was no longer enhancing.	n.r.
Khoja et al. [24]	2016	Hyperintense white matter foci in both subcortical (enhancing on FLAIR) and periventricular areas (non-enhancing). There were ovoid lesions perpendicular to the ventricles and lesions involving the corpus callosum. All lesions showed restricted diffusion. The findings were consistent with either demyelination or an ischemic process. A repeat brain MRI after 10 days of steroid treatment showed increased enhancement in the previously noted lesions and lesions involving the cortex, changes more suggestive of multiple infarctions and possibly a vascular process.	n.r.
Kazandjian et al. [25]	2016	n.r.	n.r.
Carl et al. [26]	2015	Mild microangiopathic changes, an old lacunar infarction in the right thalamus and a normal pituitary gland.	Generalised slowing with prevailing slow theta and delta waves.
Richard et al. [27]	2017	n.r.	Mild slowing and no evidence of seizure activity.
Matsuo et al. [28]	2018	High-intensity areas in the inner aspect of the temporal lobe, thalamus, cerebral aqueduct and spinal cord.	n.r.
Brown et al. [1]	2017	T2 hyperintensity of the medial temporal lobes bilaterally with contrast enhancement.	Background slowing (6–7 Hz) with intermittent delta slowing.
Feng et al. [29]	2017	FLAIR hyperintensity adjacent to the resection site, which was consistent with the postoperative changes.	Generalised, intermittent slowing consistent with mild diffuse encephalopathy.
Strik et al. [30]	2017	Small, scattered, T2 and FLAIR hyperintense contrast-enhancing lesions dorsal to the left lateral ventricle and in the midbrain and brain stem.	n.r.
Chaucer et al. [31]	2018	No evidence of metastases or lymphoreticular disorder.	n.r.
Leitinger et al. [32]	2018	Multiple and confluent cortical and subcortical FLAIR hyperintensities within both cerebral hemispheres.	Moderate slowing.
Zurko et al. [33]	2018	Diffusely oedematous cerebellum with patchy enhancement, signs of early tonsillar herniation, and early hydrocephalus.	n.r.
Kopecký et al. [34]	2018	No signs of any tumour lesion. MRI revealed a symmetrical, pathologically increased signal within the basal ganglia consistent with possible inflammatory involvement of these structures.	n.r.
De la Hoz et al. [35]	2018	No abnormalities.	n.r.
Shibaki et al. [36]	2019	T2 high signal intensity in the mesencephalon and medial thalami (typical findings in anti-Ma2-associated encephalitis).	n.r.
Zafar et al. [37]	2019	Multifocal cerebral demyelination, primarily involving the parietal lobe: multiple hyperintense T2 FLAIR signal white matter lesions, primarily in the parietal lobes but also involving the posterior frontal lobes, corpus callosum and right brachium ponti. None of these lesions were enhanced following contrast administration. No restricted diffusion was present. No significant mass effect or midline shift was identified. These findings were suggestive of acute demyelinating encephalomyelitis.	Diffuse, generalised slowing with practically no significant reactivity to external stimuli.
Gill et al. [38]	2019	T2/FLAIR hyperintensities bilaterally in the medial temporal lobes.	No seizure activity.
Hottinger et al. [39]	2018	Severe abnormalities in both hippocampi with contrast-enhancing lesions.	n.r.
Gill et al. [38]	2019	No signal abnormality or enhancement.	n.r.

EEG = electroencephalogram; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; n/a = not applicable; n.r. = not reported

Cuzzubbo et al. [2], the median (range) time of onset was 6 (1–74) weeks.

To establish a diagnosis of ICI-associated encephalitis, potential differential diagnoses must be excluded (table 4). Consultation with a neurologist is advised. Infectious aetiologies (bacterial, fungal or viral meningoencephalitis, especially herpes simplex) and leptomenigeal disease can be ruled out by analysing CSF. Typical CSF findings in patients with ICI-associated encephalitis are elevated white blood cell counts with predominant lymphocytes and ele-

vated protein concentrations. The glucose concentration is usually normal. Polymerase chain reaction assays of CSF for herpes simplex virus type 1, herpes simplex virus type 2 and varicella zoster virus must be ordered. In addition, cytological examination of CSF is recommended.

A cerebral MRI should be performed to detect brain metastases and to exclude ischemia or intracranial haemorrhage. Nonconvulsive status epilepticus must be ruled out by recording an EEG. Blood and urine cultures must be drawn. A complete blood count, a C-reactive protein test

and a comprehensive metabolic panel (including ammonia) should be obtained, and arterial blood gases should be analysed. In selected patients, especially in those not responding to corticosteroid therapy, blood concentrations of vitamins (B1, B12), thyroid-stimulating hormone and cortisol should be measured. Toxicological screening should be performed if an intoxication is suspected. Measurement of the anti-neutrophil cytoplasmic antibody concentration can help to exclude vasculitis [3, 4]. The recommended diagnostic approach is illustrated in figure 1.

### Management

The severity of neurological adverse events (nAEs) is graded from 1 to 4. In patients with grade 1 nAEs (asymptomatic or mild symptoms), ICI therapy can be continued. However, in patients with grade 2 (moderate symptoms), grade 3 (severe symptoms) and grade 4 (life-threatening symptoms) nAEs, ICIs should be stopped [27, 45].

In our experience, immune-mediated encephalitis is usually graded 3 to 4. Therefore, permanent discontinuation of ICI therapy is advisable, and treatment with corticosteroids should be established. We recommend an initial in-

**Table 3:** CSF analyses.

Case report	Year of publication	CSF cell count	CSF protein level	CSF glucose level
<b>Limmattal Hospital</b>				
See appendix 1	n/a	59/μl	589 mg/l	4.1 mmol/l
See appendix 1	n/a	n.r.	n.r.	n.r.
See appendix 1	n/a	n.r.	n.r.	n.r.
Schneider et al. [6]	2017	16/μl	1027 mg/l	1.1 mmol/l
See appendix 1	n/a	83/μl	1065 mg/l	2.7 mmol/l
<b>Literature search</b>				
Larkin et al. [4]	2017	Elevated	3120 mg/l	2.4 mmol/l
Larkin et al. [4]	2017	14/μl	850 mg/l	11.8 mmol/l
Larkin et al. [4]	2017	52/μl	n.r.	n.r.
Larkin et al. [4]	2017	n.r.	n.r.	n.r.
Larkin et al. [4]	2017	18/μl	n.r.	n.r.
Shah et al. [8]	2018	Normal	560 mg/l	Normal
Shah et al. [8]	2018	19/μl	Normal	Normal
Williams et al. [9]	2016	8/μl	Normal	Normal
Williams et al. [9]	2016	18/μl	980 mg/l	Normal
Niki et al. [10]	2016	58/μl	4460 mg/l	n.r.
Cook et al. [11]	2017	Elevated	Elevated	Normal
Kim et al. [12]	2019	Elevated	n.r.	n.r.
Mandel et al. [13]	2014	8/μl	1030 mg/l	5.6 mmol/l
Laserna et al. [14]	2018	667/μl	>6000 mg/l	5.1 mmol/l
Levine et al. [15]	2017	9/μl	1000 mg/l	4.4 mmol/l
Bossart et al. [7]	2017	n.r.	n.r.	n.r.
Arakawa et al. [16]	2019	139/μl	1320 mg/l	Normal
Salam et al. [17]	2016	17/μl	530 mg/l	n.r.
Ito et al. [18]	2017	58/μl	1280 mg/l	n.r.
Conry et al. [19]	2015	n.r.	n.r.	n.r.
Burke et al. [20]	2018	Normal	Normal	Normal
Boyd et al. [21]	2015	Normal	1370 mg/l	n.r.
Voskens et al. [22]	2013	n.r.	n.r.	n.r.
Cao et al. [23]	2016	n.r.	n.r.	n.r.
Khoja et al. [24]	2016	n.r.	270 mg/l	4.4 mmol/l
Kazandjian et al. [25]	2016	n.r.	n.r.	n.r.
Carl et al. [26]	2015	Normal	850 mg/l	Normal
Richard et al. [27]	2017	Normal	n.r.	Normal
Matsuo et al. [28]	2018	16/μl	1620 mg/l	n.r.
Brown et al. [1]	2017	Elevated	n.r.	n.r.
Feng et al. [29]	2017	0/μl	Normal	Normal
Strik et al. [30]	2017	15/μl	Normal	n.r.
Chaucer et al. [31]	2018	n.r.	n.r.	n.r.
Leitinger et al. [32]	2018	30/μl	560 mg/l	Normal
Zurko et al. [33]	2018	31/μl	1610 mg/l	4.1 mmol/l
Kopecký et al. [34]	2018	Elevated	n.r.	n.r.
De la Hoz et al. [35]	2018	136/μl	600 mg/l	2.9 mmol/l
Shibaki et al. [36]	2019	15/μl	900 mg/l	n.r.
Zafar et al. [37]	2019	74/μl	Elevated	n.r.
Gill et al. [38]	2019	3/μl	330 mg/l	6.4 mmol/l
Hottinger et al. [39]	2018	16/μl	1145 mg/l	n.r.
Gill et al. [38]	2019	10/μl	400 mg/l	n.r.

CSF = cerebrospinal fluid; n/a = not applicable; n.r. = not reported

travenous dose of 1 to 2 mg/kg body weight/day of methylprednisolone (or equivalent), as suggested in the literature [46, 47]. If symptoms persist, other diagnoses must be entertained, as shown in figure 1. In this case, an extended metabolic panel should be ordered, and paired samples of plasma and CSF should be tested for both paraneoplastic and autoimmune encephalitis antibodies. Autoimmune encephalitis antibodies can be quantified even after an initial treatment with corticosteroids [48]. Data on the time course

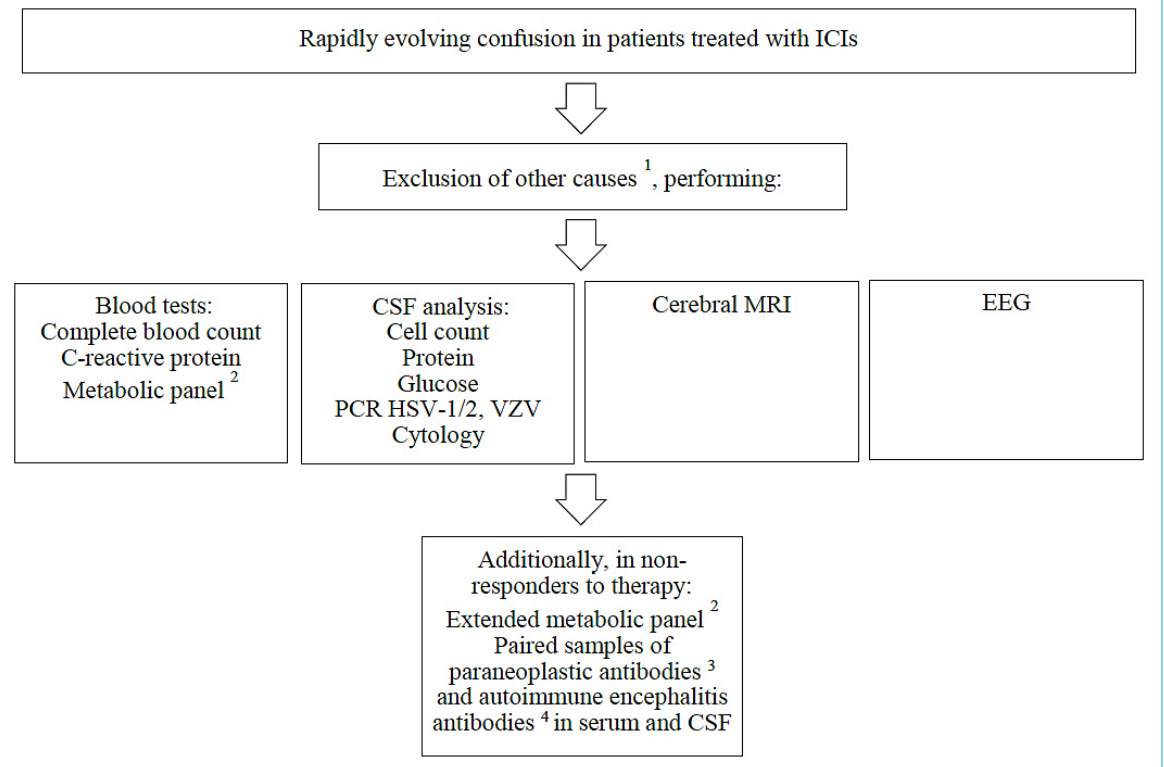
of autoimmune encephalitis or paraneoplastic antibodies before and after ICI treatment are not available, however. In the most severe cases, the corticosteroid dose can be increased to  $\geq 1000$  mg daily. Due to the long half-life of ICIs, steroids should be tapered slowly over at least four weeks. Potential adverse effects of corticosteroid therapy must be anticipated, including delirium, arterial hypertension, hyperglycaemia and lower resistance to infection. Coadministration of trimethoprim/sulfamethoxazole thera-

**Table 4:** Differential diagnosis of ICI-associated encephalitis.

Differential diagnosis	Diagnostic tests
Infection (sepsis-induced encephalopathy; bacterial, fungal or viral meningoencephalitis; brain abscess)	Blood tests including culture, CSF analysis including culture and viral PCR (herpes simplex, varicella zoster), MRI
Intracerebral haemorrhage	MRI
Ischaemia	MRI
Leptomeningeal dissemination	CSF analysis, MRI
Metabolic disturbances	Blood tests <sup>2</sup>
Nonconvulsive status epilepticus	EEG
Paraneoplastic limbic encephalitis	Blood tests <sup>†</sup> , CSF analysis <sup>‡</sup> , MRI
PRES	MRI
Vasculitis	Blood tests (ANCA), MRI

AGNA (SOX1) = anti-glia nuclear antibody; AMPAR1/2 = alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors 1 and 2; ANCA = anti-neutrophil cytoplasmic antibody; CASPR2 = contactin-associated protein-like 2; CRMP5 (CV2) = collapsin response mediator protein 5; CSF = cerebrospinal fluid; DPPX = dipeptidyl-peptidase-like protein 6; EEG = electroencephalogram; GABAR = gamma aminobutyric acid B receptor; GAD65 = glutamate decarboxylase 65 kDa isoform; gly = glycine; Hu = neuronal nuclear antibody-1; ICI = immune checkpoint inhibitor; LGI1 = leucine-rich glioma-inactivated 1; MRI = magnetic resonance imaging; NMDAR = N-methyl-D-aspartate receptor; PCR = polymerase chain reaction; PRES = posterior reversible encephalopathy syndrome; Ri (ANNA2) = neuronal nuclear antibody-2; TG = thyroglobulin; TPO = thyroid peroxidase; TR = human thrombin receptor; VGKC = voltage-gated potassium channel; Yo (PCA1) = anti-Purkinje cell cytoplasmic antibody type 1; ZIC4 = zic family member 4 \* Glucose, creatinine, bilirubin, liver enzymes, ammonia, electrolytes, arterial blood gases; additionally, in non-responders to therapy: vitamins B1/12, thyroid function tests, cortisol concentrations, toxicological screening † Antibodies against AGNA (SOX1), AMPAR1/2, amphiphysin, CRMP5 (CV2), DPPX, GABAR, GAD65, Hu (ANNA1), Ma1, Ma2, Ri (ANNA2), TG, TPO, TR, VGKC (anti-LGI1, anti-CASPR2), Yo (PCA1) and ZIC4 ‡ Antibodies against NMDAR, AMPAR1/2, VGKC (anti-LGI1, anti-CASPR2), Gly, GABAR, etc.

**Figure 1:** Diagnosis of ICI-associated encephalitis.<sup>1</sup> For differential diagnoses, see table 4.<sup>2</sup> Glucose, creatinine, bilirubin, liver enzymes, ammonia, electrolytes, arterial blood gas analysis; additionally, in non-responders to therapy: vitamins B1/12, thyroid function tests, cortisol concentration, toxicological screening, ANCA<sup>3</sup> Antibodies against AGNA (SOX1), AMPAR1/2, amphiphysin, CRMP5 (CV2), DPPX, GABAR, GAD65, Hu (ANNA1), Ma1, Ma2, Ri (ANNA2), TG, TPO, TR, VGKC (anti-LGI1, anti-CASPR2), Yo (PCA1), ZIC4<sup>4</sup> Antibodies against NMDAR, AMPAR1/2, VGKC (anti-LGI1, anti-CASPR2), Gly, GABAR, etc. ANCA = anti-neutrophil cytoplasmic antibody; CSF = cerebrospinal fluid; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; ICI = immune checkpoint inhibitor; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; VZV = varicella zoster virus





py should be considered, especially if long-term treatment is necessary. In steroid-refractory cases and after careful review of the results of (neuro-)imaging studies, blood tests, CSF analysis, EEG, and titres of paraneoplastic and autoimmune encephalitis antibodies, treatment with IVIG, plasma exchange therapy or rituximab should be considered [4, 45, 46, 49–51]. According to the case report by Hottinger et al. [39], natalizumab, an antibody directed at  $\alpha 4\beta 1$  integrin which thus limits lymphocyte recruitment to the CNS, may be considered to treat ICI-associated encephalitis. An algorithm for the management of ICI-associated encephalitis is shown in figure 2.

### Prognosis

Most patients with ICI-associated encephalitis respond to intravenous corticosteroids. Due to early diagnosis and appropriate management, the majority of patients (82%) included in this review improved significantly. However, nine patients (18%) died during their hospital stay.

### Limitations of the study

The study design is descriptive and retrospective. As there are no prospective randomised controlled trials examining the diagnosis and therapy of ICI-associated encephalitis, the current data provide the best available basis for treatment recommendations. Prospective studies are needed to identify the optimal treatment.

### Implications for further research

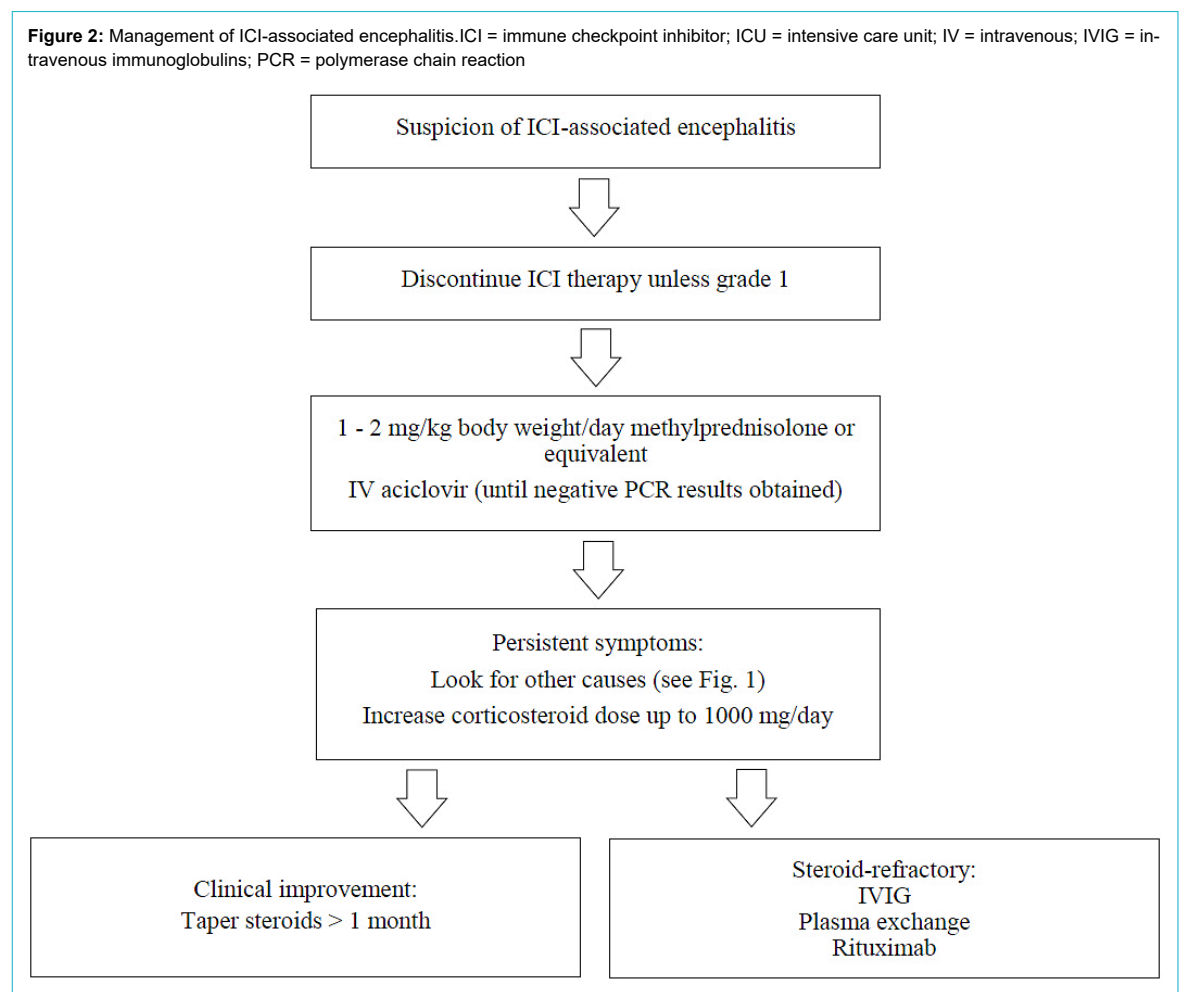
New indications for ICI therapy and combinations with other therapeutic strategies (e.g., chemotherapy) are in pre-clinical and clinical testing. The incidence of and risk factors for ICI-associated encephalitis will be reported accordingly. To date, ICI encephalitis is a diagnosis of exclusion. However, we propose that the diagnosis can be made after clinical evaluation and performing basic laboratory analysis, MRI and EEG. Expanded testing for rare autoimmune diseases of the brain should be reserved for therapy-refractory cases.

It would be interesting to study whether the concomitant administration of ICIs and corticosteroids could prevent the development of encephalitis. It remains unclear whether the presence of paraneoplastic antibodies is a risk factor for ICI-associated encephalitis, whether the antibodies are possibly induced by ICI therapy, or whether they lead to an alternative diagnosis, e.g., paraneoplastic limbic encephalitis. Further studies are needed to determine the role of paraneoplastic antibodies in ICI encephalitis.

### Conclusions

The use of ICIs for multiple tumour types is increasing. In patients treated with ICIs presenting with rapidly evolving confusion, encephalitis should be suspected. Blood tests, CSF analysis, cerebral MRI and an EEG should be ordered. The treatment of choice is intravenous corticosteroids. Steroid unresponsiveness is rare and should lead to

**Figure 2:** Management of ICI-associated encephalitis. ICI = immune checkpoint inhibitor; ICU = intensive care unit; IV = intravenous; IVIG = intravenous immunoglobulins; PCR = polymerase chain reaction



a review of the diagnosis. Alternative treatment options are IVIG, plasma exchange therapy and rituximab.

#### Potential competing interests

CP has received honoraria from Roche and MSD. The other authors declare no conflicts of interest.

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## Appendix 1

**Descriptions of the four unpublished cases****Case 1**

A 74-year-old woman with pulmonary adenocarcinoma (cT2a, Nx, cM1c, stage IVB, no brain metastases) presented to the emergency room with sudden onset of fever, confusion and a reduced level of consciousness. First-line therapy with carboplatin, pemetrexed and pembrolizumab was established 17 days before. Due to elevated inflammatory markers and opacities in a chest X-ray, pneumonia was suspected for which antibiotic treatment was started. The patient's condition continued to deteriorate. Computerised tomography (CT) of the brain, chest and abdomen did not show any signs of infection. Blood cultures were negative. Lumbar puncture revealed leucocytosis (85% monocytes) and increased values of protein (589 mg/l, normal value 150–450 mg/l), glucose (4.1 mmol/l, normal value 2.2–3.9 mmol/l) and lactate (2.9 mmol/l, normal value 1.2–2.1 mmol/L). PCR assays for herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2) and varicella zoster virus (VZV) were negative. Serological tests showed a positive IgG result and negative IgM result for tick-borne encephalitis (TBE), which was due to a vaccination. Meningoencephalitis was suspected, and the patient was transferred to the intensive care unit (ICU) with a reduced Glasgow Coma Scale (GCS) of 11. Since antibiotic and antiviral treatment (ceftriaxone, amoxicillin, metronidazole, and aciclovir) did not improve the patient's condition, an electroencephalogram (EEG) was obtained. The EEG showed focal findings in the parieto-temporal region, suggesting encephalopathy. An MRI scan of the brain did not show any signs of encephalitis or meningitis. Nevertheless, a diagnosis of immune-mediated encephalitis due to cancer treatment with pembrolizumab was established. Antimicrobial therapy was stopped, and the patient was treated with intravenous steroids (methylprednisolone, 125 mg daily) and intravenous immunoglobulins (IVIg, 30 g/300 ml). The patient's condition improved rapidly within five days in the ICU, and she was transferred back to the ward. The corticosteroid therapy was changed to oral prednisone 50 mg daily, followed by a steroid taper over several weeks. The patient was discharged from the hospital after 17 days.

**Case 2**

A 58-year-old woman with stage IV carcinosarcoma of the uterus received third-line therapy with lenvatinib and pembrolizumab. She was previously treated with carboplatin, paclitaxel and bevacizumab well as with hormonal therapy with medroxyprogesterone acetate and later tamoxifen. A solitary brain metastasis was treated with radiosurgery. She developed diffuse pain, fever, aphasia, agitation and confusion 13 days after starting the new therapeutic regimen with pembrolizumab. She was intubated and transferred to the intensive care unit. A CT scan of the brain did not show signs of intracerebral haemorrhage or another new pathology. Neurology consultation was obtained. Herpes simplex encephalitis or limbic encephalitis were suspect-

ed, and treatment with aciclovir and methylprednisolone (80 mg IV) was established. Furthermore, the dose of her seizure prophylaxis with levetiracetam was increased. A brain MRI, electroencephalogram (EEG) and analysis of CSF were not performed. The patient's condition promptly improved with steroid treatment, and she was transferred back to the ward after 3 days. Due to further progression of the carcinosarcoma with infiltration of the ureters with consecutive severe renal failure, further cancer treatment was stopped, and the regimen changed to palliation. The patient died a couple of days later.

**Case 3**

A 63-year-old woman with advanced pulmonary adenocarcinoma (cT1, cN2, M1c, UICC stage IV without brain metastases) that had progressed despite chemotherapy with carboplatin and pemetrexed was treated with nivolumab. The patient developed muscle weakness and dysarthria after approximately 10 months. She was admitted to the emergency room with a reduced level of consciousness but without fever. An MRI scan of the brain that was performed in the rehabilitation clinic prior to hospitalisation did not reveal signs of ischaemia, encephalitis or meningitis. An electroneuromyography (ENMG) study did not show signs of myositis or demyelinating polyneuropathy. An EEG was not obtained, and CSF was not analysed. Clinically, autoimmune encephalitis was suspected, and the patient received intravenous steroids (125 mg of methylprednisolone daily), which led to a clear improvement of her condition. Steroid treatment was changed to oral prednisone, and the patient was discharged home after 11 days in the inpatient ward with a steroid taper regimen.

**Case 4**

A 79-year-old man with stage IV Merkel-cell carcinoma was brought to the emergency room with aphasia, visual disturbance and memory loss. There was no sign of intracerebral haemorrhage, aneurysm or vascular stenosis in the CT scan of the brain. Brain MRI did not detect encephalitis, hypophysitis, or ischaemia. An EEG showed mild background slowing with moderate focal slowing over the left temporal region but no epileptiform activity. CSF analysis revealed an increased cell count (83/μl, normal value <5/μl) with 90% monocytes, an increased level of protein (1065 mg/l, normal value 150–450 mg/l) and a normal concentration of glucose (2.7 mmol/l, normal value 2.2–3.9 mmol/l). The patient was treated with fourth-line therapy with ipilimumab and nivolumab, which was started 12 days prior to admission. Previously, he received cisplatin/etoposide, avelumab and talimogene laherparepvec. Due to a clinical diagnosis of encephalitis, intravenous immunosuppressive therapy with 125 mg methylprednisolone was initiated, and the patient was transferred to the ICU. Additionally, the patient received aciclovir until the PCR assays for HSV-1, HSV-2 and VZV were negative. Given the rapid improvement of his clinical condition, intravenous methylprednisolone was changed to oral prednisone and tapered over a few weeks. The patient was discharged from the ICU and the hospital after three and six days, respectively.