

1 **Supplementary Tables 1-5**

2 **Supplementary Table 1: Additional clinical features and details of the index case at**
 3 **presentation**

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Measurements, results, clinical actions	Features of lumbar puncture	
	Value	Reference values and notes
<i>Nucleated cells/μL</i>	590	
<i>Neutrophils</i>	80%	
<i>Lymphocytes</i>	6%	
<i>Glucose</i>	67 mg/dl	Reference: 45-75
<i>Protein</i>	135 mg/dl	Reference: 15-40
<i>Negative results</i>	Bacterial cultures, HSV-1/2 PCR, cytology, paraneoplastic panels	
<i>Medication administered</i>	Broad spectrum antibiotics, acyclovir	

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6 **Supplementary Table 2: Characteristics of 22 cases of ICI-induced meningoencephalitis**

Age (years; median, range)	65 (26-83)
Female gender	6 (27)
Primary cancer melanoma	20 (91)
Agent	
Anti-PD-1/PD-L1 monotherapy	6 (27)
Ipilimumab monotherapy	6 (27)
Anti-PD-1 + ipilimumab	10 (44)
Prior brain metastases?	5 (23)
Active brain metastases?	2 (9)
Prior brain surgery?	2 (9)
Prior brain radiation	2 (9)
Neurologic co-morbidities	7 (32)*
Prior autoimmune disease	3 (14)
Time to onset (days, median, range)	80 (4-684)
Anti-PD-1/PD-L1 monotherapy	86 (5-684)
Ipilimumab monotherapy	58 (39-138)
Anti-PD-1 + ipilimumab	93 (4-517)
Symptoms	
Confusion	11 (50)
Headaches	8 (36)
Seizures	5 (23)
Fever	4 (18)
Focal neurologic deficits	5 (23)
Concurrent irAEs	
None	10 (44)
Colitis/enteritis	3 (14)
Thyroiditis	3 (14)

Rash	3 (14)
Other	3 (14) [#]
MRI findings	
Unremarkable	16 (73)
Findings present	6 (27) ^{**}
Cerebrospinal fluid analysis	
Nucleated cells/mL (median, range)	37 (2-590)
Hospitalized	20 (91)
Multiple hospitalizations	5 (23)
Length of stay (days; median, range)	6.5 (2-120)
Treatments	
High dose steroids	19 (86)
Pulse dose (e.g. 1g/daily)	3 (14)
1-2mg/kg	16 (73)
Intravenous immunoglobulin	4 (18)
Other (Plasma exchange, rituximab)	2 (9)
Outcome	
Resolved	15 (68)
Persistent symptoms	5 (22)
Fatal	2 (9) ^{##}

*Includes seizure disorder (N=3), cerebrovascular accident (N=2), migraines, cerebral arteriovenous formation. [#]Hypophysitis, hepatitis, and epididymitis. ^{**}Enhancement of temporal lobes (N=3), enhancement of occipital lobes (N=2), perivascular enhancement in caudate/putamen/internal capsule (N=1), cranial nerve enhancement (N=1). ^{##}Both in patients with MRI findings

Supplementary Table 3: Cases of non-immunotherapy-induced encephalitis assessed for EBNA1 staining, NanoString DSP, and RNA-seq

Diagnosis	Age/Sex	Pathology notes	EBNA1+ (% cells)	PD-L1+ (% cells)
Chronic meningoencephalitis consistent with clinical history of atypical Rasmussen's encephalitis	50/F	Relatively mild inflammation	0	0
Meningoencephalitis with anti-calcium channel antibodies. CMV identified reactive cells present ^c	40/M		0	5
Toxoplasmosis	34/M	Small sample	0	0
Progressive Multifocal Leukoencephalopathy (JC virus infection)	62/F	Very small sample	0	2
Demyelinating process (multiple sclerosis)	25/F		0	0
Rasmussen's encephalitis ^b	3/M		0	0
Autoimmune encephalitis of unknown etiology ^a	50/M	Relatively mild inflammation	0	1
Acute hemorrhagic leukoencephalitis (variant of acute disseminated encephalomyelitis)	63/M		0	0
Rasmussen's encephalitis	5/F		0	5

^a Non-ICI-encephalitis (1) in **Figure 2**

^b Non-ICI-encephalitis (2) in **Figure 2**

^c Non-ICI-encephalitis (3) in **Figure 2**

18 **Supplementary Table 4: HLA haplotype of the index case**

Locus	Allele 1 / Allele 2
<i>HLA-A</i>	02:01:01 / 02:01:01
<i>HLA-B</i>	39:01:01 / 51:01:01
<i>HLA-C</i>	12:03:01 / 14:02:01
<i>HLA-DQA</i>	01:02:01 / 05:01:01
<i>HLA-DQB</i>	02:01:01 / 06:04:01
<i>HLA-DRB1</i>	03:01:01 / 13:02:01
<i>HLA-DRB3</i>	01:01:02 / 03:01:01
<i>HLA-DPB1</i>	03:01:01 / 04:01:01

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20 **Supplementary Table 5: TCRs containing the [PSGS] motif are viral-specific and not**

21 **associated with autoimmune reactivity**

CDR3	TRBV gene	TRBJ gene	HLA restriction	Epitope	Epitope origin	PMID
CASSVAPSGSESPLHF	V9*01	J1-6*01	HLA-DRA*01	PKYVKQNTLKLAT	InfluenzaA	12466894
CASRPSGSELIYEQYF	V5-1*01	J2-7*01	HLA-A*02	GILGFVFTL	InfluenzaA	28423320
CASSPPSGSAYNEQFF	V9*01	J2-1*01	HLA-B*07:02	LPRRSGAAGA	InfluenzaA	28636589
CAISDPSGSSYNEQFF	V10-3*01	J2-1*01	HLA-B*07:02	RPRGEVRFL	HSV-2	20139278
CASSPPSGSYEQYF	V7-9*01	J2-7*01	HLA-B*08	FLKEKGGL	HIV-1	17287271
CASSQEPSGSWGEQYF	V3-1*01	J2-7*01	HLA-A*02	CINGVCWTV	HCV	28146579
CASSQEPSGSWGEQYF	V3-1*01	J2-7*01	HLA-A*02	CINGVCWTV	HCV	28146579
CASSQEPSGSWGEQYF	V3-1*01	J2-7*01	HLA-A*02	CINGVCWTV	HCV	28146579
CASSPPSGSGFNEQFF	V18*01	J2-1*01	HLA-A*02:01	GLCTLVAML	EBV	12504586
CASSSDPSGSIAYEQYF	V5-1*01	J2-7*01	HLA-B*08:01	RAKFKQLL	EBV	24512815
CASSPPSGSYEQYF	V7-9*01	J2-7*01	HLA-A*02	NLVPMVATV	CMV	28423320
CSAPSGSSYEQYF	V20-1*01	J2-7*01	HLA-A*02	NLVPMVATV	CMV	28423320

CATSRVPSGSYEQYF	V15*01	J2-7*01	HLA-A*02	NLVPMVATV	CMV	28423320
CASSLVPSGSTDTQYF	V5-1*01	J2-3*01	HLA-A*02:01	NLVPMVATV	CMV	28636589

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