Neurologic autoimmunity and immune checkpoint inhibitors

Autoantibody profiles and outcomes

Elia Sechi, MD, Svetomir N. Markovic, MD, Andrew McKeon, MD, Divyanshu Dubey, MD, Teerin Liewluck, MD, Vanda A. Lennon, MD, PhD, A. Sebastian Lopez-Chiriboga, MD, Christopher J. Klein, MD, Michelle Mauermann, MD, Sean J. Pittock, MD, Eoin P. Flanagan, MD, and Anastasia Zekeridou, MD, PhD

Neurology® 2020;95:e2442-e2452. doi:10.1212/WNL.0000000000010632

Correspondence

Dr. Zekeridou
zekeridou.anastasia@mayo.edu

MORE ONLINE

Video

Abstract

Objective

To describe neural autoantibody profiles and outcomes in patients with neurologic autoimmunity associated with immune checkpoint inhibitor (ICI) cancer immunotherapy.

Methods

In this retrospective descriptive study, 63 patients with ICI-related neurologic autoimmunity were included: 39 seen at the Mayo Clinic Neurology Department (clinical cohort) and 24 whose serum/CSF was referred to the Mayo Clinic Neuroimmunology Laboratory for autoantibody testing. Serum/CSF samples were tested for neural-specific autoantibodies. Predictors of unfavorable outcome (residual adverse event severity grade ≥ 3) were explored (logistic regression).

Results

Median age at neurologic symptom onset was 65 years (range 31–86); 40% were female. Neurologic manifestations were CNS-restricted ($n = 26$), neuromuscular ($n = 30$), combined ($n = 5$), or isolated retinopathy ($n = 2$). Neural-specific autoantibodies were common in patients with CNS involvement (7/13 [54%] in the unbiased clinical cohort) and included known or unidentified neural-restricted specificities. Only 11/31 patients with CNS manifestations had neuroendocrine malignancies typically associated with paraneoplastic autoimmunity. Small-cell lung cancer (SCLC)–predictive antibodies were seen in 3 patients with non-neuroendocrine tumors (neuronal intermediate filament immunoglobulin G [IgG] and antineuronal nuclear antibody 1 with melanoma; amphiphysin IgG with non-SCLC). A median of 10 months from onset (range, 0.5–46), 14/39 in the clinical cohort (36%) had unfavorable outcomes; their characteristics were age ≥ 70 years, female, CNS involvement, lung cancer, higher initial severity grade, and lack of systemic autoimmunity. By multivariate analysis, only age remained independently associated with poor outcome ($p = 0.01$). Four of 5 patients with preexistent neurologic autoimmunity experienced irreversible worsening after ICI.

Conclusions

Neural-specific autoantibodies are not uncommon in patients with ICI-related CNS neurologic autoimmunity. Outcomes mostly depend on the pre-ICI treatment characteristics and clinical phenotype.

From the Departments of Neurology (E.S., A.M., D.D., T.L., V.A.L., C.J.K., M.M., S.J.P., E.P.F., A.Z.), Oncology (S.N.M.), Laboratory Medicine and Pathology (A.M., D.D., V.A.L., S.J.P., E.P.F., A.Z.), and Immunology (V.A.L.), Mayo Clinic, Rochester, MN; and Department of Neurology (A.S.L.-C.), Mayo Clinic, Jacksonville, FL.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AChR = acetylcholine receptor; **ANNA** = antineuronal nuclear antibody; **BDUMP** = bilateral diffuse uveal melanocytic proliferation; **CRMP5** = collapsin response-mediator protein 5; **CTLA4** = cytotoxic T-lymphocyte-associated antigen-4; **GAD65** = glutamic acid decarboxylase 65; **GFAP** = glial fibrillary acidic protein; **HMGCR** = β -hydroxy- β -methylglutaryl coenzyme-A reductase; **ICI** = immune checkpoint inhibitor; **IgG** = immunoglobulin G; **IVIg** = IV immunoglobulin; **LGII** = leucine-rich glioma-inactivated 1; **MG** = myasthenia gravis; **NIF** = neuronal intermediate filament; **NMDAR** = NMDA receptor; **PCA** = Purkinje cell antibody; **PD1** = programmed death-1; **PDL1** = programmed death-1 ligand; **PRES** = posterior reversible encephalopathy syndrome; **SCLC** = small-cell lung carcinoma; **SRP** = signal recognition particle; **STR** = striational autoantibodies; **UNA** = autoantibodies as yet unidentified molecularly; **VGCC** = voltage-gated calcium channels; **VGKC** = voltage-gated potassium channel.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy.^{1,2} By targeting negative regulatory steps of T-cell activation, namely the cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) and programmed death-1 (PD1) or its ligand (PDL1), they enhance endogenous immune responses including antitumor immunity.¹⁻³ An undesired outcome is autoimmunity that can potentially affect any organ (dermatologic, gastrointestinal, endocrine, and pulmonary autoimmunity are most common), with an overall frequency of 15%–90% for all severity grades in single-agent trials.⁴ Neurologic autoimmunity of all grades is estimated to occur in 4.2% of patients receiving monotherapy and up to 14% of patients treated with a combination of CTLA4 and PD1/PDL1 inhibitors.^{5,6} Neuromuscular manifestations are the most common, accounting for approximately two-thirds of patients, while CNS involvement is less frequent and often extends beyond the classic paraneoplastic phenotypes, making diagnosis and management challenging.⁷⁻¹¹ In particular, otherwise extremely rare neural autoantibodies seem to occur more frequently in patients with cancer treated with ICI and not always with their typical cancer association.¹⁰ In addition, novel neural autoantibodies are increasingly recognized in these patients.^{12,13} A systematic investigation of the neural autoantibody profiles accompanying the different neurologic phenotypes and underlying cancers is lacking. In this study, we report the neural autoantibody profiles and outcome predictors in a large cohort of ICI-treated patients with autoimmune neurologic complications.

Methods

Standard protocol approvals, registrations, and patient consents

The study was approved by the Mayo Foundation Institutional Review Board. Patients consented to the use of their medical records for research.

Patients

Two patient cohorts were retrospectively identified through August 31, 2019: a clinical cohort and a laboratory cohort.

The clinical cohort comprises patients seen in the Mayo Clinic Neurology Department with a diagnosis of ICI-related

neurologic autoimmunity and neurologic adverse event severity grade ≥ 2 . Medical records were reviewed and patients with other plausible explanations for their neurologic symptoms were excluded (e.g., brain metastasis, recent exposure to chemotherapeutic agents known to be potentially neurotoxic). Neurologic adverse event severity grades for specific manifestations were as previously defined (grade 1, asymptomatic or mild; grade 2, minimal, noninvasive intervention indicated; grade 3, severe, not immediately life-threatening; grade 4, life-threatening, urgent intervention indicated; grade 5, death).¹⁴ Severity grades were independently assessed (A.Z., E.S.) at presentation of neurologic autoimmunity and last clinical follow-up; consensus was reached after discussion in case of disagreement. Twenty patients were reported previously.^{5,12,15-19}

The laboratory cohort includes patients whose serum or CSF were referred to the Mayo Clinic Neuroimmunology Laboratory for neural autoantibody testing. Clinical information was obtained from physicians on notification of antibody positivity and in providing antibody profile interpretation.

Neural autoantibody testing

Autoantibody screening evaluations were performed by clinically validated methods in the Mayo Clinic Neuroimmunology Laboratory and were based on patients' presenting phenotype.²⁰ Patients with neuromuscular junction disorders or myopathy underwent autoantibody testing for muscle acetylcholine receptor (AChR) and sarcomeric protein specificities (striational autoantibodies [STR; titer $<1:7,680$ were excluded]). A minority of patients with myopathy had antibody testing for β -hydroxy- β -methylglutaryl coenzyme-A reductase (HMGCR) and signal recognition particle (SRP) antibodies (outside laboratory).

Patients with CNS or peripheral nerve involvement underwent a paraneoplastic evaluation (serum or CSF) that includes autoantibodies specific for muscle and ganglionic AChR, STR, voltage-gated potassium channel (VGKC) complex, glutamic acid decarboxylase 65 (GAD65; serum titer >20 nmol/L or CSF titer >0.02 nmol/L were included), voltage-gated calcium channels (VGCCs, P/Q-type or N-type), and screening by indirect immunofluorescence assay on a composite of mouse tissues that detects classic autoantibodies (antineuronal nuclear antibody [ANNA] 1, ANNA2, ANNA3, Purkinje cell antibody

[PCA] 1, PCA2/MAP1B, PCA-Tr, amphiphysin, collapsin response-mediator protein 5 [CRMP5], and anti-gial nuclear antibody 1/SOX1), recently described neural autoantibodies (specific for phosphodiesterase 10A [PDE10A], neuronal intermediated filaments [NIF]) plus additional neural-specific autoantibodies as yet unidentified molecularly (UNA).²⁰ In patients with encephalopathy, autoantibodies specific for leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein (CASPR) 2, NMDA receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), γ -aminobutyric acid B receptor, and glial fibrillary acidic protein (GFAP) α were also tested.

Statistical analysis and outcome

Continuous and categorical variables were reported as median (range) and number (percentage), respectively. Univariate logistic regression analysis was used to investigate variables associated with unfavorable outcome in the clinical cohort, defined as a residual adverse event severity grade ≥ 3 at last follow-up. The simultaneous effect of variables found to be significantly associated with unfavorable outcome was explored by multivariate logistic regression (JMP Pro 14.1.0). Odds ratios and 95% confidence intervals were reported; p values < 0.05 were considered statistically significant.

Data availability

Anonymized data used for this study are available upon reasonable request from the corresponding author.

Results

Sixty-three patients were included: clinical cohort, 39; laboratory cohort, 24. Their demographics, oncologic characteristics, specific ICI treatment received, and neurologic phenotypes are summarized in table 1. In 5 patients (clinical cohort, 4; laboratory cohort, 1), the autoimmune neurologic manifestations were already present at the time of ICI treatment. In the clinical cohort, the majority of symptoms in patients without preexisting neurologic autoimmunity occurred within the first 3 months of ICI treatment (25/35; 71%).

CNS manifestations

CNS manifestations, observed in 31 patients (clinical cohort, 13; laboratory cohort, 18; table 2), included encephalopathy with or without seizures ($n = 21$), cerebellar ataxia ($n = 11$), hyperkinetic movement disorders ($n = 3$), optic neuropathy ($n = 4$), myelopathy ($n = 3$), or combinations thereof. Only 11/31 patients with CNS manifestations had neuroendocrine tumors, while the rest had malignancies not typically associated with paraneoplastic autoimmunity. Encephalitis manifestations were either localized (e.g., limbic or basal ganglia restricted) or diffuse. Concomitant posterior reversible encephalopathy syndrome (PRES) and fasciculations developed in an LGI1 immunoglobulin G (IgG) seropositive patient. Two patients with CSF positivity for GFAP α IgG had, as anticipated, a steroid-responsive meningoencephalitis.²¹ In a patient with high GAD65 IgG levels, limbic encephalitis appeared after new onset of type 1 diabetes.

Among 20 patients with available CSF data, 19 (95%) had abnormalities: lymphocytic pleocytosis, 14 (median cell count, 25; range, 8–76); CSF-restricted oligoclonal bands, 9.

MRI abnormalities, noted in 11/18 (61%) with available information, included localized T2 hyperintensities (e.g., mesiotemporal, basal ganglia, spinal cord), parenchymal/meningeal enhancement, or focal atrophy (e.g., cerebellum). MRI findings were consistent with the patients' clinical syndromes (figure, A–D). ¹⁸F-Fluorodeoxyglucose PET revealed diffuse or focal areas of hypometabolism or hypermetabolism in 2 patients with limbic encephalitis; 2 additional patients (both lacking CSF biomarkers for Alzheimer disease) had diffuse and frontotemporal hypometabolism, respectively (table 2).

Neuromuscular manifestations

Thirty-four patients had neuromuscular symptoms. Peripheral neuropathy was most common ($n = 22$; clinical cohort, 19; laboratory cohort, 3), in isolation ($n = 14$) or accompanied by myopathy ($n = 4$) or CNS manifestations ($n = 4$). Isolated neuralgic amyotrophy developed in 4 patients (unilateral brachial plexopathy, 2; bilateral phrenic nerve palsy presenting with acute dyspnea, 2). Five patients had a subacute length-dependent polyradiculoneuropathy (both axonal and demyelinating, 4; pure axonal, 1). Two patients had diffuse acute inflammatory demyelinating polyneuropathy with facial nerve involvement. Two patients had biopsy-proven vasculitic neuropathy (figure, E) and improved minimally or not at all after ICI discontinuation or immunosuppression/immunomodulation. Other neuropathy phenotypes included isolated cranial neuropathy (excluding optic neuritis; $n = 5$) or other nonspecified neuropathies ($n = 4$).

Three patients had clinical generalized myasthenia gravis (MG): clinical cohort, 1; laboratory cohort, 2. In one of these patients, the disease was known before ICI treatment initiation and this was the only patient with MG who tested positive for muscle AChR IgG.

Myopathy developed in 13 patients (clinical cohort, 11; laboratory cohort, 2) and predominantly involved bulbar muscles ($n = 5$), proximal limb muscles ($n = 5$), or was confined to the extraocular muscles ($n = 1$). The 2 remaining patients had diffuse myopathy causing diaphragmatic paralysis with respiratory failure in one. Serum creatine kinase was elevated in 8/12 (67%) with available data (median 680 U/L [range 72–13,000]). Troponin was elevated in 8 patients, with decreased ejection fraction by echocardiography in 4. Muscle biopsy, available for 6 patients, contained multifocal areas with necrotic and regenerating fibers ($n = 4$; figure, F) or mild inflammation ($n = 2$).

Other clinical manifestations

Three patients (clinical cohort) had ICI-related hypophysitis before or coinciding with onset of neurologic manifestations; 17 patients (45%) had other preexisting or coinciding

Table 1 Characteristics of 63 patients with neurologic immune-related adverse events associated with immune checkpoint inhibitor (ICI) therapy

	Clinical cohort (n = 39)	Laboratory cohort (n = 24)
Demographics		
Age at neurologic symptom onset, y	65 (31–86)	65.5 (40–84)
Female sex	14 (36)	11 (46)
Cancer diagnosis		
Melanoma ^a	20 (51)	7 (29)
Lung carcinoma	8 (21)	10 (42)
SCLC	5/8	3/10
Renal cell carcinoma	4 (10)	1 (4)
Breast/ovarian carcinoma	3 (8)	0
Esophageal carcinoma	2 (5)	0
Peritoneal mesothelioma	1 (3)	0
Non-Hodgkin lymphoma	1 (3)	0
Merkel cell carcinoma	1 (3)	2 (8)
Prostate carcinoma	0	1 (4)
Bladder carcinoma	0	1 (4)
Hepatocellular carcinoma	0	1 (4)
Uterus neuroendocrine neoplasm	0	1 (4)
ICIs		
PD-1/PDL-1	31 (79)	14 (58)
CTLA-4	1 (3)	3 (13)
Combined	7 (18)	4 (17)
Unknown agent	0	3 (13)
Interval from ICI start to first neurologic symptom		
Months	2 (0–16)	NA
Cycles, n	3 (1–20)	NA
Neurologic manifestations		
CNS	10 (26)	16 (67)
Neuromuscular	24 (62)	6 (25)
CNS + neuromuscular	3 (8)	2 (8)
Retinopathy	2 (5)	0
Adverse event severity		
Grade 4	6 (15)	14 (58)
Grade 3	21 (54)	7 (29)
Grade 2	12 (31)	3 (13)

Abbreviations: CTLA4 = cytotoxic T-lymphocyte-associated antigen-4; PD1 = programmed death-1; PDL1 = programmed death-1 ligand; SCLC = small-cell lung cancer.

Values are median (range) or n (%).

^a One patient had coexisting melanoma and ovarian cancer.

nonneurologic autoimmunity (e.g., thyroiditis, myocarditis, pneumonitis, hepatitis, colitis). Two patients had isolated autoimmune retinopathy: (1) bilateral diffuse uveal melanocytic proliferation (BDUMP) in a 60-year-old man with esophageal junction adenocarcinoma treated successfully with IV immunoglobulin (IVIg), high-dose steroids, and plasmapheresis; and (2) preexisting melanoma-associated retinopathy in a 75-year-old woman who worsened after pembrolizumab and improved following IVIg and bevacizumab.

Autoantibody profile

Of 31 patients with CNS involvement, 24 patients (77%) had detectable neural-specific autoantibodies. Neural antibodies with known antigenic specificities were seen in 16/24 (67%) (serum, 4; CSF, 6; both, 6): ANNA1, 3; CRMP5, 3; amphiphysin, 2; GFAP, 2; NIF, 2; PDE10A, 2; SOX1, 1; LGI1, 1; GAD65, 1; NMDAR, 1; with or without coexisting low-titer serum VGKC, 3; P/Q-type VGCC, 2; and N type VGCC, 2. In 9 patients (38%), the neural-specific antibodies detected were of yet unidentified molecular specificities (serum, 2; CSF, 6; both, 1), including one with coexisting SOX1 and P/Q-type VGCC autoantibodies. In the unbiased clinical cohort, the frequency of any neural-specific autoantibody among patients with CNS involvement was 54% (7/13 patients; 1/7 had an isolated UNA [CSF of a patient with limbic encephalitis]).

Of 22 patients with peripheral nerve involvement, 9 were positive for the following: ANNA1, 3; LGI1, 1; UNA, 1; muscle AChR, 3; and STR, 3. Of these patients, 7 had concomitant CNS manifestations (all ANNA1 or LGI1-IgG positive) or myopathy (muscle AChR or STR autoantibody positive). One patient (muscle AChR IgG seropositive) had isolated oculomotor neuropathy per the referring provider that could represent an ocular myopathy and an UNA-seropositive patient with limited information had unspecified neuropathy (both patients were from the laboratory cohort).

All patients with MG or myopathy (n = 16) were tested for STR autoantibodies and 9 were positive; 5 of them had coexisting muscle AChR. All seropositive patients had myopathy except for one who had preexisting MG before ICI treatment. In the unbiased clinical cohort, 6/11 (55%) patients with myopathy were seropositive for muscle AChR and/or STR autoantibodies; 4 muscle AChR binding autoantibodies showed modulation. None of 8 patients with myopathy who were tested for SRP or HMGCR autoantibodies was positive.

A “classical” paraneoplastic association (i.e., clinical, oncologic, and autoantibody profiles typical of what is classically recognized as paraneoplastic) was observed in 6 patients: 5 of them had small-cell lung carcinoma (SCLC) and IgGs specific for amphiphysin and P/Q-type VGCC with preexisting cerebellar ataxia (n = 1); SOX1, P/Q-type VGCC, and UNA (n = 1) with limbic encephalitis; ANNA1 and CRMP5 (n = 1) with preexisting cerebellar ataxia, myelitis, and peripheral neuropathy (video 1); CRMP5 (n = 1) with a longitudinally extensive myelopathy; and ANNA1 and STR (n = 1) with limbic

Table 2 Clinical, radiologic, and laboratory characteristics of 31 immune checkpoint inhibitor (ICI)-recipient patients with CNS complications: clinical cohort (cases 1–13) and laboratory cohort (cases 14–31)

N/age, y/ sex	Cancer	ICI type	Neurologic presentation	CNS imaging	CSF	Intervention	Neurologic outcome (follow-up, mo)	IgG specificity (specimen)
1/57/M	Renal cell	Nivolumab	PRES, fasciculations, pain	MRI: posterior vasogenic edema	NA	ICI D/C	PRES resolved; persistent fasciculations (2)	LG11 (serum)
2/56/M	Melanoma	Pembrolizumab	Meningoencephalitis, bilateral ON, cerebellar ataxia	MRI: optic nerve hyperintensity and enhancement	WBC 76, P 74 mg/dL	ICI D/C, IVMP, PLEX, RTX	Cognition improved; imbalance persisted (21)	None (serum and CSF)
3/71/F	Melanoma and ovarian	Nivolumab	Encephalitis, ataxia	FDG-PET/CT, diffuse hypometabolism; frontotemporal atrophy	WBC N, P 48 mg/dL, OCB 9	ICI D/C, IVMP, OS	Marked improvement; relapsed during steroid taper (9)	None (serum and CSF)
4/58/F	Melanoma	Nivolumab + pembrolizumab	Limbic encephalitis, headache, nausea and vomiting	MRI: N	WBC 43, P N, OCB none	ICI D/C	Mild improvement; residual cognitive impairment (3)	None (serum and CSF)
5/75/F	Renal cell cancer	Pembrolizumab	Hyperkinetic movement disorder	MRI: figure, A	WBC and P N, OCB 8	ICI D/C, OS, IVMP, PLEX	Moderate improvement; residual dyskinesia (27)	PDE10A (serum and CSF)
6/71/M	Non-SCLC	Pembrolizumab	Cerebellar ataxia	MRI: figure, B	NA	ICI D/C	Moderate improvement; residual dysarthria and gait imbalance (17)	None (serum and CSF)
7/70/F	SCLC	Preexisting autoimmunity, nivolumab	Cerebellar ataxia	MRI: mild generalized atrophy	NA	ICI D/C, PLEX	Worsened after 1 cycle of nivolumab; died, pneumonia with respiratory failure (4)	Amphiphysin, VGCC (serum)
8/70/F	SCLC	Nivolumab	Encephalitis	MRI: diffuse atrophy > hippocampal; FDG-PET: frontotemporal hypometabolism	WBC 8, P 85 mg/dL, OCB none	ICI D/C, unspecified steroids	No improvement, severe residual cognitive impairment (17)	None (serum and CSF)
9/56/M	Melanoma	Nivolumab + ipilimumab; prior pembrolizumab	Two myelitis episodes and unilateral ON (3 months apart); with severe visual deficit ^a	MRI: optic nerve enhancement; MS-like T2-hyperintense spinal cord lesions (x2)	WBC and P N, OCB none	ICI D/C, IVMP, OS	Improved with steroids therapy; relapsed after cessation; minimal residual weakness (7)	None (serum and CSF)
10/51/M	SCLC	Preexisting autoimmunity, nivolumab	Cerebellar ataxia, encephalomyelitis, peripheral neuropathy	CT: nonspecific diffuse volume loss	WBC 19, P 47 mg/dL, OCB 4	ICI D/C, IVMP, IVlg, PLEX, CYC	Worsened after 3 cycles of nivolumab, wheelchair bound (16)	ANNA1, CRMP5 (serum and CSF)
11/63/F	SCLC	Atezolizumab	Progressive myelopathy	MRI: spine tractopathy with enhancement	WBC 46, P 105 mg/dL	IVMP, ICI D/C, CYC	Improvement (7)	CRMP5, (serum and CSF)
12/70/F	Melanoma	Preexisting autoimmunity, nivolumab	Limbic encephalitis	MRI: figure, C; FDG-PET: mesial temporal lobe hypermetabolism	WBC 20, OCB >5	ICI D/C	Worsened after 6 cycles of nivolumab, severe cognitive impairment (8)	UNA (CSF)
13/62/F	SCLC	Atezolizumab	Limbic encephalitis, cerebellar ataxia, hearing loss, ON	MRI: Mesial temporal lobe T2-hyperintensity; FDG-PET: figure, D	WBC 25, P 80 mg/dL, OCB 6	ICI D/C, IVMP, CYC	Mild improvement (1)	ANNA1, striational (serum)
14/68/F	Non-SCLC	Nivolumab	Encephalitis	NA	Reported N	NA	No improvement	Amphiphysin (serum)
15/65/F	Non-SCLC	Nivolumab	Meningoencephalitis	NA	WBC elevated	NA	NA	UNA (serum)
16/64/F	Non-SCLC	NS	Encephalitis	NA	NA	NA	NA	UNA (CSF)

Continued

Table 2 Clinical, radiologic, and laboratory characteristics of 31 immune checkpoint inhibitor (ICI)-recipient patients with CNS complications: clinical cohort (cases 1–13) and laboratory cohort (cases 14–31) (*continued*)

N/age, y/ sex	Cancer	ICI type	Neurologic presentation	CNS imaging	CSF	Intervention	Neurologic outcome (follow-up, mo)	IgG specificity (specimen)
17/47/F	Renal cell	Nivolumab	Encephalitis, seizures, dysautonomia	MRI: negative	WBC elevated	IVMP, PLEX	Marked improvement	None (serum and CSF)
18/66/F	Non-SCLC	Nivolumab	Hemiballismus	MRI: bilateral basal ganglia T2 hyperintensity	OCB 16, P 56 mg/dL	ICI D/C, IVMP, PLEX, RTX	No improvement, death from neurologic deterioration	PDE10A (serum and CSF)
19/61/M	Melanoma, non-SCLC	NS	Encephalitis	NA	NA	NA	NA	UNA (CSF)
20/45/M	Melanoma	NS	Cerebellar ataxia	MRI: negative	WBC 15	IVMP	Mild improvement	NIF (serum)
21/71/M	Melanoma	CTLA-4 antibody	Ataxia and movement disorder	NA	NA	NA	NA	UNA (serum)
22/74/F	Merkel cell	Pembrolizumab	Ataxia, encephalitis, and ON	NA	WBC and OCB elevated	NA	NA	CRMP5, NIF (serum and CSF)
23/58/M	SCLC	PD-1 antibody	Limbic encephalitis (after onset DM1)	NA	NA	IVMP, IVIg	Resolved	GAD65 (serum and CSF)
24/66/M	SCLC	PD-1 antibody	Limbic encephalitis	NA	NA	IVMP, IVIg	Marked improvement	VGCC (serum), Sox1, UNA (CSF)
25/60/M	SCLC	PD-1 antibody	Encephalitis and ataxia	NA	NA	NA	NA	UNA (CSF)
26/40/M	Melanoma	Tremelimumab	Meningoencephalitis	NA	NA	PLEX, OS	Improved after steroids	GFAP (CSF)
27/73/F	Non-SCLC	Pembrolizumab	Encephalitis	NA	P 50 mg/dL	Unspecified steroids	Mild improvement	UNA (CSF)
28/59/F	Neuroendocrine	Pembrolizumab	Limbic encephalitis	MRI: mesial temporal lobe and basal ganglia T2 hyperintensity	WBC 25, P 49 mg/dL	NA	NA	UNA (serum and CSF)
29/56/M	Melanoma	Nivolumab + ipilimumab	Cerebellar ataxia and peripheral neuropathy	NA	WBC 11, P 50 mg/dL	Unspecified steroids	Moderate improvement of ataxia	ANNA-1 (CSF)
30/60/F	Non-SCLC	Pembrolizumab	Meningoencephalitis	NA	30 WBC	IVMP	Improved, but relapsed after steroid cessation	GFAP (CSF)
31/79/F	Merkel cell	Pembrolizumab; prior avelumab	Limbic encephalitis	NA	WBC N, OCB 7	ICI D/C, IVMP, RTX	Significant improvement but residual cognitive deficit	NMDAR (CSF)

Abbreviations: ANNA1 = anti-neuronal nuclear antibody-1 ("anti-Hu"); CRMP5 = collapsin-response mediator protein 5; CYC = cyclophosphamide; D/C = discontinued; DM1 = type 1 diabetes; FDG = ¹⁸F-fluorodeoxyglucose; GAD65 = glutamic acid decarboxylase 65; GFAP = glial fibrillary acidic protein; IgG = immunoglobulin G; IVIg = IV immune globulins; IVMP = IV methylprednisolone; LGI1 = leucine-rich glioma-inactivated 1; N = normal; NA = data not available; NIF = neuronal intermediate filament; NMDAR = NMDA receptor; OCB = supernumerary oligoclonal bands; ON = optic neuritis; OS = oral steroids; P = proteins; PD1 = programmed death-1; PDE10A = phosphodiesterase 10A; PLEX = plasma exchange; PRES = posterior reversible encephalopathy syndrome; RTX = rituximab; SCLC = small-cell lung carcinoma; UNA = neural-specific autoantibody of unknown molecular specificity; VGCC = voltage-gated calcium channel, P/Q type; WBC = white blood cells.

In the laboratory cohort patients (14–31), ICI D/C was not known where not mentioned.

^a This patient tested negative on serum for both aquaporin-4 IgG and myelin oligodendrocyte glycoprotein IgG by live cell-based assay.

Figure Brain neuroimaging and nerve and muscle biopsies from patients with immune checkpoint inhibitor–related neurologic autoimmunity

(A–D) Brain MRI. (A) Axial image shows basal ganglia fluid-attenuated inversion recovery (FLAIR) hyperintensities, affecting the putamen and caudate head bilaterally, in a patient with phosphodiesterase 10A antibodies and hyperkinetic movements. (B) Sagittal T1-weighted image shows atrophy of the superior cerebellar vermis in a patient with seronegative autoimmune ataxia. (C) Axial imaging shows bilateral mesial temporal pole FLAIR hyperintensities, more prominent on the left, in a patient with limbic encephalitis and autoantibodies as yet unidentified molecularly. (D) ^{18}F -Fluorodeoxyglucose PET axial images show hypometabolism of the temporal poles in a patient with limbic encephalitis, ataxia, optic neuritis, and antineuronal nuclear antibody 1 antibodies. (E) Nerve biopsy of the left sural nerve of a patient with ICI-related vasculitic neuropathy demonstrates a large perivascular epineurial inflammatory collection with infiltration and disruption of the blood vessel wall: hematoxylin & eosin (H&E) (E.a) and CD45 (E.b) stain. (F) Muscle biopsy of a patient with ICI-related myopathy: H&E-stained section (F.a) shows regenerating (arrowhead) and necrotic fibers invaded by macrophages (arrows). Macrophages appear red on acid phosphatase-stained section (F.b).

encephalitis, cerebellar ataxia, and cranial neuropathy. The sixth patient had Merkel cell carcinoma with NIF IgG and CRMP5 IgG and encephalitis, ataxia, and vision changes.

Among 9 patients with CNS manifestations and neuroendocrine tumors (without preexisting autoimmunity), only 1 patient was antibody negative, 4 had SCLC-predictive antibody specificities (ANNA1, CRMP5, NIF, P/Q-type VGCC, SOX1), 1 had GAD65 IgG, 1 had NMDAR IgG, and 2 had UNAs only, without other well-described neural antibodies. SCLC-predictive antibody profiles were seen in 2 patients with melanoma and CNS manifestations (NIF IgG and ANNA1) and 1 with non-SCLC (amphiphysin IgG).

Disease course and outcome

Thirty-four patients in the clinical cohort discontinued ICI therapy before or at neurologic symptom onset (87%). Thirty-one patients (79%) received immunosuppression/immunomodulation for their neurologic syndrome: oral corticosteroids, 23; high-dose IV steroids, 18; IVIg, 11; and plasmapheresis, 8. The 5 patients who continued their ICI therapy after neurologic symptom onset had lower adverse event severity grade at onset (median, 2 [range, 2–3]) compared to patients who discontinued ICI (median, 3 [range, 2–4]; $p = 0.02$; Wilcoxon rank sum test). Their clinical phenotypes were as follows: (1) a 60-year-old man with BDUMP and esophageal junction adenocarcinoma who received monthly IVIg (0.4 g/kg) in concomitance with pembrolizumab for 17 months with

improvement of visual symptoms but cancer progression; (2) a 62-year-old man with metastatic melanoma and bilateral hearing loss after one cycle of pembrolizumab who was treated with prednisone 70 mg/d for 7 days with minimal improvement (required hearing aid 4 years later); pembrolizumab was continued for 15 months with cancer remission; (3) a 69-year-old man with melanoma and severe headache and loss of taste and hearing after 5 cycles of nivolumab and ipilimumab, treated with oral prednisone (60 mg daily for 1 week, then slow taper) with symptom resolution; nivolumab was continued for 10 months with cancer remission; (4) a 75-year-old man with recurrent melanoma and brachial plexopathy with right hemidiaphragm palsy after one cycle of nivolumab; no immunosuppression was used but there was mild spontaneous improvement; nivolumab was continued for 8 months with cancer remission; (5) a 63-year-old woman with small cell lung cancer and CRMP5 IgG progressive myelopathy after 3 cycles of atezolizumab treated with IVMP and cyclophosphamide with improvement of neurologic symptoms; an additional dose of atezolizumab was given and the patient is in cancer remission (patient 11 in table 2).

After a median follow-up of 10 months (range, 0.5–46), 14/39 patients (36%) showed unfavorable neurologic outcomes (residual severity grade ≥ 3) including 2 deaths from neurologic complications; 13 patients (33%) had favorable neurologic outcomes (severity grade = 1). Three patients relapsed after immunosuppressive therapy was tapered or discontinued

(encephalitis, 1; CNS demyelination, 1; and proximal myopathy, 1). The patients with unfavorable outcome had encephalitis/ataxia, 8; vasculitic neuropathy, 2; bulbar myopathy, 2; generalized myopathy with diaphragmatic involvement, 1; or generalized MG, 1.

Of all the variables investigated by univariate logistic regression analysis (table 3), the following were found to be significantly associated with unfavorable outcome: onset age ≥ 70 years, female sex, CNS involvement, lung cancer, higher severity grade at onset, shorter follow-up, and absence of preceding or accompanying non-neurologic ICI-related autoimmunity. By multivariate analysis, only onset age ≥ 70 years remained independently associated with poor outcome ($p = 0.01$; table 3).

Preexisting neurologic autoimmunity

Five patients had evidence of neurologic autoimmunity before ICI therapy began. Three had clinically recognized paraneoplastic syndromes affecting the CNS (cerebellar ataxia with amphiphysin IgG, P/Q-type VGCC IgG, and SCLC; encephalomyelitis, cerebellar ataxia, and peripheral neuropathy with ANNA1 IgG and CRMP5 IgGs and SCLC; and limbic encephalitis with UNA IgG and melanoma). All of these patients had irreversible neurologic worsening after ICI initiation and did not improve following immunosuppressive therapy (table 2; video 1). One patient with muscle AChR IgG-positive MG worsened after ICI, requiring bilevel positive airway pressure ventilation despite immunosuppressive/immunomodulatory therapy. The single patient who improved with immunosuppression/immunomodulatory therapy had autoimmune retinopathy and had initially worsened on starting ICI therapy.

Discussion

We provide a comprehensive analysis of patients with cancer with ICI-related neurologic autoimmunity, their associated clinical–autoantibody profiles, and outcomes. Our findings suggest that neural autoantibodies are not infrequent in patients with CNS involvement and represent useful diagnostic tools to confirm neurologic autoimmunity. The main determinants of neurologic outcome relate to the patients' baseline characteristics at ICI initiation and the phenotype of the neurologic complication.

As typically observed in patients with spontaneous paraneoplastic neurologic disorders, ICI-related neurologic complications are heterogeneous, can affect any level of the neuraxis, and can often coexist.³ Despite previous reports suggesting a low frequency of neural autoantibodies in patients with ICI-related neurologic autoimmunity, in our unbiased clinical cohort, 54% had a detectable neural autoantibody.^{5,6,22–26} We found a relatively high proportion of neural autoantibodies that have only recently been characterized (e.g., neuronal intermediate filament, PDE10A) or remain of unknown molecular specificity.^{12,16} These autoantibodies are not detectable when

Table 3 Univariate logistic regression analysis exploring potential associations with unfavorable outcome (residual adverse event severity grade ≥ 3) at last clinical follow-up

Variable	N (%) or median (range)	OR (95% CI)	<i>p</i> Value
Age ≥ 70 years ^a	15/39 (38)	5.7 (1.37–23.76)	0.01
Female	14/39 (36)	4.2 (1.04–17.14)	0.04
Melanoma	20/39 (51)	0.59 (0.16–2.21)	0.43
Lung cancer (any type)	8/39 (21)	8.6 (1.44–51.72)	0.01
ICI first-line cancer treatment	22/39 (56)	0.67 (0.18–2.49)	0.55
Adverse event severity grade at onset	3 (2–4)	4.6 (1.3–16.1)	0.01
Systemic ICI-related autoimmunity	15/39 (38)	0.15 (0.03–0.83)	0.02
CNS involvement	13/39 (33)	5.3 (1.26–22.57)	0.02
Myopathy	11/39 (28)	0.58 (0.13–2.67)	0.48
Peripheral or cranial neuropathy	19/39 (49)	0.7 (0.19–2.59)	0.58
ICI treatment cycles, <i>n</i>	3 (1–20)	1.13 (0.95–1.34)	0.13
Received immunosuppressive/modulating treatment	31/39 (79)	0.25 (0.05–1.25)	0.08
Days from neurologic symptoms onset to immunosuppression/modulation ^b	14.5 (2–360)	0.99 (0.98–1.01)	0.8
Follow-up duration, mo	10 (0.5–46)	0.89 (0.81–0.98)	<0.01
Unfavorable outcome	14/39 (36)	—	—

Abbreviations: CI = confidence interval; ICI = immune checkpoint inhibitor; OR = odds ratio.

^a When the simultaneous effect of variables found to be significantly associated with unfavorable outcome was assessed by multivariate logistic regression, only age ≥ 70 remained independently associated with unfavorable outcome at last clinical follow-up: $p = 0.01$. The age cutoff value of 70 years was obtained with a receiver operating characteristic curve using age as a continuous variable to predict unfavorable outcome, and corresponded to the largest area under the curve (0.65).

^b Patients with preexisting neurologic autoimmunity were not included.

testing is restricted to antigen-specific molecular assays. This underscores the benefit of including a neural tissue–based immunohistochemical screening assay in testing for suspected neurologic autoimmunity or other unbiased neural autoantibody detection methodologies.

The majority of neural autoantibodies we detected in this study are specific for intracellular antigens and are not directly pathogenic but rather represent biomarkers of a cytotoxic T-cell response of the same specificity. Antibody-mediated neural dysfunction with autoantibodies targeting neural synapse antigens was also noticed, as in the case of LGI1 and NMDAR autoimmunity (table 2). ICIs act by

Table 4 Summary of neurologic syndromes reported in the context of immune checkpoint inhibitor therapy

CNS^a disorders
Meningitis
Meningoencephalitis
Encephalopathy (all)
Limbic encephalitis
Brainstem encephalitis
PRES
MERS
Movement disorders
Hyperkinetic
Cerebellar ataxia
Inflammatory demyelinating/MS
Optic neuritis
Myelitis
Granulomatous inflammation
Neurosarcoidosis
Tolosa-Hunt
CNS vasculitis
Neuromuscular disorders
Muscle
Inflammatory/necrotizing myopathy
Neuromuscular junction ^b
Myasthenia gravis
LEMS
Peripheral nerve
Guillain Barré syndrome/CIDP
Axonal sensory/motor/mixed neuropathies
Vasculitic neuropathy/mononeuritis multiplex
Dysautonomia
Plexopathy/Parsonage-Turner ^c
Polyradiculoneuropathy
Sensory neuropathy
Mononeuritis/multiple cranial neuropathies
Other
Vogt-Koyanagi-Harada
Retinopathy

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; LEMS = Lambert-Eaton myasthenic syndrome; MERS = mild encephalopathy with reversible splenic lesion; MS = multiple sclerosis; PRES = posterior reversible encephalopathy syndrome.

^a Specific neural autoantibodies reported up to August 2019 (including the present study): SOX-1 (anti-glia nuclear antibody 1), amphiphysin, ANNA1 (anti-neuronal nuclear antibody 1), ANNA2 (MAP2/antineuronal nuclear antibody 2), aquaporin-4, CASPR2 (contactin-associated protein 2), CRMP5 (CV-2) (collapsin response-mediator protein 5), GAD65 (glutamic acid decarboxylase 65), glial fibrillary acidic protein, LGI1 (leucine-rich glioma-inactivated protein 1), Ma2, neuronal intermediate filament, NMDA receptor, phosphodiesterase 10A.

^b Specific neural autoantibodies reported: muscle nicotinic acetylcholine receptor and voltage-gated calcium channel, P/Q-type.

^c Ranging from complete brachial/lumbar plexopathy to isolated phrenic nerve palsy.

enhancing endogenous immune responses both at the priming and effector phase of the immune response and do not limit their effects only to cytotoxic T cells but also helper, regulatory T cells and B cells among others.^{1,2} This is consistent with the variety of clinical phenotypes and underlying disease mechanisms that are observed in ICI-treated patients, including direct T-cell or antibody cytotoxicity, granulomatous inflammation, or other not yet completely understood mechanisms (e.g., immune-mediated blood–brain barrier dysfunction in patients who develop PRES).

A classic paraneoplastic association (i.e., clinical, oncologic, and autoantibody profiles typical of what is classically recognized as paraneoplastic) was observed in 6 patients, consistent with an augmented anticancer immune response against onconeural antigens.³ However, the tumors encountered in the majority of seropositive patients are not typically accompanied by paraneoplastic neurologic syndromes (e.g., renal cell cancer, melanoma), suggesting an increased/altered neoantigen expression by the tumor under immune attack.²⁷ In addition, SCLC-predictive antibodies were present in patients with melanoma and non-SCLC. With growing therapeutic indications for ICI administration, we anticipate accelerated discovery of onconeural antigens of immunologic significance beyond the classically recognized paraneoplastic autoantigens (such as Hu proteins in SCLC).

In this study, patients with CNS involvement who were seropositive for recognized neural autoantibodies generally presented with a syndromic manifestation of the autoantibody (e.g., NMDAR/ANNA1 with encephalitis, CRMP5 with progressive myelopathy), although atypical or overlapping presentations were sometimes observed (e.g., LGI1 autoimmunity with typical peripheral involvement and coexisting PRES). Aquaporin-4 IgG has been reported in the context of ICI therapy, but the single patient in our cohort who had relapsing demyelinating disease was seronegative and fulfilled clinical criteria for multiple sclerosis diagnosis.²⁸ Multiple sclerosis has been reported previously as being triggered/worsened by ICI, by potentiation of a preexisting immune response in the CNS that was not paraneoplastic.²⁹ Other CNS manifestations that have been reported with ICI therapy include sarcoidosis/CNS granulomatosis,³⁰ vasculitis,³¹ mild encephalopathy with reversible splenic lesion,³¹ and Vogt-Koyanagi-Harada syndrome (table 4).³²

The severity and outcome of peripheral nerve and muscle manifestations were generally related to the specific clinical phenotype (e.g., ocular myopathy vs diffuse vasculitic neuropathy).⁹ In contrast with earlier reports, neuralgic amyotrophy was relatively common in this study.²² Diaphragmatic dysfunction, observed in 4 patients, manifested as severe respiratory impairment due to direct myopathic involvement or phrenic nerve paralysis and sometimes was the sole clinical manifestation. Two patients significantly improved after discontinuing ICI and immunosuppressive therapy (IV high-dose methylprednisolone and IVIg, 1; plasmapheresis, IVIg, and cyclophosphamide, 1), while mild spontaneous improvement was observed in 1 patient who continued ICI and received no immunosuppression over months.

Patients with myopathy had a prominent oculo-bulbar presentation and 4 were seropositive for muscle AChR IgG but lacked electrophysiologic evidence of MG.²⁵ Muscle AChR IgG, even though potentially pathogenic, has been described in patients without clinical MG, including patients who develop myopathy from ICI therapy, and might represent a biomarker of the underlying malignancy expressing muscle AChR under immune attack as an onconeural antigen.^{33,34} The lack of neurologic disease in the presence of potentially pathogenic antibodies could be due to titer or fine specificity of the antibody present during an evolving humoral immune response.³⁵ P/Q VGCC IgG seropositive Lambert-Eaton myasthenic syndrome has been described as an ICI complication but was not encountered in our cohort (table 4).³⁶

The final neurologic outcome was unfavorable in one-third of patients and associated with a patient's pre-ICI treatment characteristics (older age, female sex, lung cancer, and presence of systemic ICI-related autoimmunity) and clinical phenotype (CNS involvement, severity grade at onset). Patients with preexistent paraneoplastic CNS autoimmunity and neural autoantibody seropositivity had a particularly severe neurologic deterioration after commencing ICI that was generally poorly responsive to protracted immunotherapy. These patients underscore the utility of neural autoantibody screening before ICI initiation in the presence of unexplained neurologic symptoms, and urge caution in using ICIs in patients with preexisting neurologic autoimmunity and onconeural antibodies.^{3,34} On the contrary, the benefit of neural autoantibody screening in all patients who are initiating ICI treatment (and related costs) needs to be determined. There might be a role for screening in patients with tumors traditionally associated with neural autoantibodies even when neurologically asymptomatic, such as SCLC and thymoma.^{20,35} To this effect, in a small study of patients with thymoma undergoing ICI treatment, the presence of neural autoantibodies before ICI initiation predicted the development of autoimmune complications.³⁴

This study is limited by its retrospective nature and small sample size that did not allow stratification of patients by

clinical phenotype, associated neural antibodies, and treatment modality (most patients were treated nonuniformly with immunosuppression/immunomodulation). Our findings are generalizable to similar populations with moderate to severe neurologic manifestations (we only included patients seen in the neurology department with severity grade ≥ 2), thus the neural autoantibody frequencies and outcomes could be different outside this context. Future studies will clarify optimal treatment strategies for patients with ICI-related neurologic autoimmunity.

Acknowledgment

The authors thank the Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology, which supported this project with a Research Fellowship assigned to E.S.

Study funding

No targeted funding reported.

Disclosure

E. Sechi reports no disclosures relevant to the manuscript. S. Markovic reports a grant from Vavotar Life Sciences. A. McKeon reports research support from Euroimmun. D. Dubey has a patent pending for KLHL11 as a marker of neurologic autoimmunity; received research support from Grifols, Center of Multiple Sclerosis and Autoimmune Neurology, and Center for Clinical and Translational Science; and consulted for UCB and Astellas. All compensation for consulting activities is paid directly to Mayo Clinic. T. Liewluck reports no disclosures relevant to the manuscript. V. Lennon reports royalty payments from RSR/Kronus. A. Lopez-Chiriboga reports no disclosures relevant to the manuscript. C. Klein is a consultant for Pfizer and Stealth Pharmaceutical with no personal monies received; and reports Ackea Honorarium for a talk on Fabry disease. M. Mauermann reports research support from IONIS and Alnylam. S. Pittcock reports personal fees, nonfinancial support, and other from Alexion and MedImmune. All compensation was paid directly to the Mayo Clinic. He received personal compensation for attending the UCB Advisory Board meeting on September 10, 2019, and reports grant/research support from Alexion, Grifols, MedImmune, and AEA. All compensation is paid to Mayo Clinic. He reports issued patents 8,889,102, NMO Autoantibodies as a Marker for Neoplasia; and 9,891,219B, Methods for Treating NMO by Administration of Eculizumab to an Individual That is AQP4+. E. Flanagan reports research support as a site principal investigator in a randomized placebo-controlled clinical trial of inebilizumab (a CD19 inhibitor) in neuromyelitis optica spectrum disorders funded by MedImmune/Viela Bio. A. Zekeridou has a patent pending on PDE10A IgG as a biomarker of neurologic autoimmunity. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Publication history

Received by *Neurology* February 25, 2020. Accepted in final form May 27, 2020.

Appendix Authors

Name	Location	Contribution
Elia Sechi, MD	Mayo Clinic, Rochester, MN	Designed and conceptualized the study, drafted the manuscript and figure, analyzed and interpreted the data
Svetomir N. Markovic, MD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
Andrew McKeon, MD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
Divyanshu Dubey, MD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
Teerin Liewluck, MD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
Vanda A. Lennon, MD, PhD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
A. Sebastian Lopez-Chiriboga, MD	Mayo Clinic, Jacksonville, FL	Interpreted the data, revised the manuscript for intellectual content
Christopher J. Klein, MD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
Michelle Mauermann, MD	Mayo Clinic, Rochester, MN	Interpreted the data; revised the manuscript for intellectual content
Sean J. Pittock, MD	Mayo Clinic, Rochester, MN	Interpreted the data, revised the manuscript for intellectual content
Eoin P. Flanagan, MD	Mayo Clinic, Scottsdale, AZ	Interpreted the data, revised the manuscript for intellectual content
Anastasia Zekeridou, MD, PhD	Mayo Clinic, Rochester, MN	Designed and conceptualized the study, analyzed and interpreted the data, revised the manuscript for intellectual content, study supervision

References

- Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252–264.
- Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med* 2012;366:2517–2519.
- Zekeridou A, Lennon VA. Neurologic autoimmunity in the era of checkpoint inhibitor cancer immunotherapy. *Mayo Clin Proc* 2019;94:1865–1878.
- Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol* 2017;8:49.
- Kao JC, Liao B, Markovic SN, et al. Neurological complications associated with anti-programmed death 1 (PD-1) antibodies. *JAMA Neurol* 2017;74:1216–1222.
- Spain L, Walls G, Julve M, et al. Neurotoxicity from immune-checkpoint inhibition in the treatment of melanoma: a single centre experience and review of the literature. *Ann Oncol* 2017;28:377–385.

- Brown MP, Hissaria P, Hsieh AH, Kneebone C, Vallat W. Autoimmune limbic encephalitis with anti-contactin-associated protein-like 2 antibody secondary to pembrolizumab therapy. *J Neuroimmunol* 2017;305:16–18.
- Gill A, Perez MA, Perrone CM, Bae CJ, Pruitt AA, Lancaster E. A case series of PD-1 inhibitor-associated paraneoplastic neurologic syndromes. *J Neuroimmunol* 2019;334:576980.
- Johansen A, Christensen SJ, Scheie D, Hojgaard JLS, Kondziella D. Neuromuscular adverse events associated with anti-PD-1 monoclonal antibodies: systematic review. *Neurology* 2019;92:663–674.
- Vogrig A, Fouret M, Joubert B, et al. Increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e604.
- Williams TJ, Benavides DR, Patrice KA, et al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. *JAMA Neurol* 2016;73:928–933.
- Zekeridou A, Kryzer T, Guo Y, et al. Phosphodiesterase 10A IgG: a novel biomarker of paraneoplastic neurologic autoimmunity. *Neurology* 2019;93:e815–e822.
- Titulaer MJ, Irani SR, Lassmann H. PDE10A antibodies in autoimmune encephalitis: a possible marker of cancer immunotherapy? *Neurology* 2019;93:327–328.
- Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018;36:1714–1768.
- Alhammad RM, Dronca RS, Kotschade LA, et al. Brachial plexus neuritis associated with anti-programmed cell death-1 antibodies: report of 2 cases. *Mayo Clin Proc Innov Qual Outcomes* 2017;1:192–197.
- Basal E, Zaleski N, Kryzer TJ, et al. Paraneoplastic neuronal intermediate filament autoimmunity. *Neurology* 2018;91:e1677–e1689.
- Liewluck T, Kao JC, Mauermann ML. PD-1 inhibitor-associated myopathies: emerging immune-mediated myopathies. *J Immunother* 2018;41:208–211.
- Ruff MW, Mauermann ML. The Mayo Clinic experience with the neurological complications of the CTLA-4 inhibitor ipilimumab. *Neurologist* 2018;23:98–99.
- Kunchok A, Zekeridou A, Pittock S. CRMP5-IgG-associated paraneoplastic myelopathy with PD-L1 inhibitor therapy. *JAMA Neurol Epub* 2019 Jan 1.
- Zekeridou A, Majed M, Heliopoulos I, Lennon VA. Paraneoplastic autoimmunity and small-cell lung cancer: neurological and serological accompaniments. *Thorac Cancer* 2019;10:1001–1004.
- Fang B, McKeon A, Hinson SR, et al. Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. *JAMA Neurol* 2016;73:1297–1307.
- Dubey D, David WS, Amato AA, et al. Varied phenotypes and management of immune checkpoint inhibitor-associated neuropathies. *Neurology* 2019;93:e1093–e1103.
- Fellner A, Makranz C, Lotem M, et al. Neurologic complications of immune checkpoint inhibitors. *J Neurooncol* 2018;137:601–609.
- Mancone S, Lycan T, Ahmed T, et al. Severe neurologic complications of immune checkpoint inhibitors: a single-center review. *J Neurol* 2018;265:1636–1642.
- Suzuki S, Ishikawa N, Konoeda F, et al. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. *Neurology* 2017;89:1127–1134.
- Wilson R, Menassa DA, Davies AJ, et al. Seronegative antibody-mediated neurology after immune checkpoint inhibitors. *Ann Clin Transl Neurol* 2018;5:640–645.
- Schreiber RD, Old LJ, Smyth MJ. Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011;331:1565–1570.
- Narumi Y, Yoshida R, Minami Y, et al. Neuromyelitis optica spectrum disorder secondary to treatment with anti-PD-1 antibody nivolumab: the first report. *BMC Cancer* 2018;18:95.
- Gerdes LA, Held K, Beltran E, et al. CTLA4 as immunological checkpoint in the development of multiple sclerosis. *Ann Neurol* 2016;80:294–300.
- Murphy KP, Kennedy MP, Barry JE, O'Regan KN, Power DG. New-onset mediastinal and central nervous system sarcoidosis in a patient with metastatic melanoma undergoing CTLA4 monoclonal antibody treatment. *Oncol Res Treat* 2014;37:351–353.
- Cuzzubbo S, Javeri F, Tissier M, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. *Eur J Cancer* 2017;73:1–8.
- Crosson JN, Laird PW, Debiec M, Bergstrom CS, Lawson DH, Yeh S. Vogt-Koyanagi-Harada-like syndrome after CTLA-4 inhibition with ipilimumab for metastatic melanoma. *J Immunother* 2015;38:80–84.
- Touat M, Maissonobe T, Knauss S, et al. Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer. *Neurology* 2018;91:e985–e994.
- Mammen AL, Rajan A, Pak K, et al. Pre-existing antiacetylcholine receptor autoantibodies and B cell lymphopenia are associated with the development of myositis in patients with thymoma treated with avelumab, an immune checkpoint inhibitor targeting programmed death-ligand 1. *Ann Rheum Dis* 2019;78:150–152.
- Zekeridou A, McKeon A, Lennon VA. Frequency of synaptic autoantibody accompaniments and neurological manifestations of thymoma. *JAMA Neurol* 2016;73:853–859.
- Nakatani Y, Tanaka N, Enami T, Minami S, Okazaki T, Komuta K. Lambert-Eaton myasthenic syndrome caused by nivolumab in a patient with squamous cell lung cancer. *Case Rep Neurol* 2018;10:346–352.