Neurologic Autoimmunity in the Era of Checkpoint Inhibitor Cancer Immunotherapy

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Abstract

Neurologic autoimmune disorders in the context of systemic cancer reflect antitumor immune responses against onconeural proteins that are autoantigens in the nervous system. These responses observe basic principles of cancer immunity and are highly pertinent to oncological practice since the introduction of immune checkpoint inhibitor cancer therapy. The patient’s autoantibody profile is consistent with the antigenic composition of the underlying malignancy. A major determinant of the pathogenic outcome is the anatomic and subcellular location of the autoantigen. IgGs targeting plasma membrane proteins (eg, muscle acetylcholine receptor-IgG in patients with paraneoplastic myasthenia gravis) have pathogenic potential. However, IgGs specific for intracellular antigens (eg, antineuronal nuclear antibody 1 [anti-Hu] associated with sensory neuronopathy and small cell lung cancer) are surrogate markers for CD8\(^+\) T lymphocytes targeting peptides derived from nuclear or cytoplasmic proteins. In an inflammatory milieu, those peptides translocate to neural plasma membranes as major histocompatibility complex class I protein complexes. Paraneoplastic neurologic autoimmunity can affect any level of the neuraxis and may be mistaken for cancer progression. Importantly, these disorders generally respond favorably to early-initiated immunotherapy and cancer treatment. Small cell lung cancer and thymoma are commonly associated with neurologic autoimmunity, but in the context of checkpoint inhibitor therapy, other malignancy associations are increasingly recognized.

Cancer immunotherapy was the “Holy Grail” for 20th century tumor immunologists. The initial goal was to develop cancer-specific therapeutic antibodies. Subsequent studies sought cytotoxic T cells specific for cancer-derived peptide antigens. In the same period, clinical-serologic correlative observations made in patients with neurologic disease who had paraneoplastic autoimmune syndromes revealed incontrovertible evidence for robust spontaneous antitumor responses that, although rare, appeared to limit cancer spread.\(^1,2\) These responses against onconeural proteins recognize nervous system—restricted autoantigens in healthy adult tissues (Figure 1). Spontaneous paraneoplastic disorders are usually subacute in onset. The incorporation of autoimmune serologic testing into neurology practice has revealed diverse paraneoplastic neurologic manifestations. Examples include atypical movement disorders, seizures, sleep disturbance, cognitive/behavioral deficits, and disrupted gastrointestinal motility.\(^3,4\) The initial diagnosis can be mistaken for a neurodegenerative, infectious, demyelinating, or psychiatric disorder or a manifestation of presumed cancer progression. Fortunately, paraneoplastic autoimmune neurologic disorders have the potential to respond favorably to appropriate early-initiated immunotherapy and treatment of the underlying cancer.

Neural autoantibodies validated as cancer biomarkers are rarely found in healthy individuals.\(^5,7,9\) Autoantibodies identifiable in a patient’s serum or spinal fluid aid the diagnosis of both autoimmunity and cancer and guide optimal therapy.\(^5,7\) Evolving autoantibody specificities and levels detected in longitudinal serologic surveillance may herald tumor recurrence. Determination of a patient’s baseline serological profile holds promise for...
monitoring responses to checkpoint inhibitor therapy, and for predicting neurological complications, especially in treating cancers noted for neurological autoimmune complications.10

IMMUNOLOGIC MECHANISMS OF PARANEOPLASTIC AUTOIMMUNITY

General Principles
Paraneoplastic autoimmune neurologic disorders are indicative of an antitumor immune response. A patient’s serum profile of neural autoantibodies reflects the antigens expressed in the tumor. Before cancer is clinically evident, its antigenicity evolves through an immunoediting process that limits its spread.11 In the “elimination phase” of this response, innate and subsequently adaptive effectors of immune surveillance detect and destroy neoplastic cells. An “equilibrium phase” of tumor dormancy ensues, in which mutated “non-self” antigens stimulate an initially competent adaptive effector response that restricts cancer cell proliferation.11 The patient typically presents to the oncologist in the “escape phase” of this response. Having overcome containment by the immune system, the tumor is symptomatic. Factors favoring a tumor’s escape from immune elimination include its loss of a critical antigen (reducing recognition by cytotoxic T cells), down-regulation of major histocompatibility complex class I (MHC1), deficient peptide loading (eg, by mutation of the transporter of antigenic peptides protein), and acquired resistance to cytotoxic effector mechanisms (eg, by enhanced expression of a Bcl2-like apoptosis regulator).11

An effective adaptive immune response against cancers expressing self-epitopes has the potential to initiate autoimmunity (Figure 2). Self- and non-self-antigens (ie, mutated or aberrantly processed peptides) are released from tumors under initial attack by innate immune responders (eg, natural killer cells). These antigens are able to activate antigen-specific T and B lymphocytes. The display of non-self-peptide “neoantigens” on antigen-presenting cells allows self-tolerant T cells to be bypassed. CD4+ helper T cells primed via the major histocompatibility complex class II (MHC2) pathway activate antigen-specific B cells to differentiate into plasma cells. These antigen-specific plasma cells secrete high-affinity antibodies against both the mutated epitope and linked nonmutated (self-) epitopes in the oncoprotein.12 Cross-presentation of a neoantigen via the MHC1 pathway primes CD8+ cytotoxic T cells, which migrate from the lymph node to the tumor site. There, the T cells encounter and kill cancer cells by engaging their antigen receptors with cancer MHC1 proteins displaying inciting peptide antigens.12,13 IgG autoantibodies, produced in parallel with CD8+ T cells of the same antigen specificity, likely sustain and augment the response by delivering to antigen-presenting cells opsonized intracellular proteins released from lysed tumor cells. Activation of antigen-specific B cells similarly amplifies the adaptive immune response through the internalizing, via B-cell antigen receptors, of cognate proteins released by lysed tumor cells. Immunoproteosome processing creates some peptides with cryptic neoepitopes for presentation to T cells.
directly and in a “cross” manner. An immune response progressing in the highly immuno- genic environment of a tumor’s draining lymph node would promote activation of helper T cells by nonmutated (self-) peptides through the process of epitope spreading.\(^4,12\)

The ability of neoepitopes on onconeural proteins to bypass self-tolerant T cells was demonstrated in a study of patients with paraneoplastic scleroderma and an associated RNA polymerase III subunit—specific autoantibody, RPC1-IgG.\(^4\) Cancers from RPC1-IgG—seropositive patients with contemporaneous scleroderma diagnosis and from control patients with a serologically distinct form of scleroderma and remote cancer history were evaluated genetically. A subclonal cell population with RPC1 somatic mutation or heterozygosity loss was found in 75% of RPC1-IgG—positive patients’
tumors but in no control tumor. Only RPC1-IgG–positive patients’ sera immunoprecipitated RPC1 proteins, both native and mutant. Further, patient CD4+ T cells were activated by both mutated and native RPC1 peptides predicted by computer algorithm to bind to the patients’ MHC2 molecules. Somatic mutations of the genes encoding cdr2 and cdr2l (Purkinje cell cytoplasmic autoantigens) have similarly been found in ovarian carcinomas from patients with paraneoplastic cerebellar degeneration. In addition, multiple messenger RNA transcripts encoding potential mutated forms of the muscle acetylcholine receptor (AChR) α1 subunit polypeptides were found in a small cell lung carcinoma (SCLC) of a patient with paraneoplastic myasthenia gravis.

**Neurologic Paraneoplastic Autoimmunity**

Organ-restricted autoimmune damage is mediated by IgG or by cytotoxic T lymphocytes. A major determinant of the pathophysiologic outcome is the autoantigen’s subcellular location. Neural-specific autoantigens defined by paraneoplastic IgGs reside in the nucleus, cytoplasm, or plasma membrane of neurons, glia, or skeletal muscle. IgGs specific for an intracellular onco-neural antigen do not exert cell-specific cytotoxicity but serve as surrogate biomarkers for effector T cells. CD8+ cytotoxic T cells target cells displaying on their surface membranes MHC1-complexed peptides derived from intracellular proteins (Figure 3A). Under the influence of interferon-γ, the cell’s proteasome switches its enzyme composition from housekeeping to immunoproteasome type. Peptides generated by the constitutive proteasome maintain peripheral tolerance. By contrast, peptide fragments generated from self-proteins through immunoproteasome cleavage potentially yield cryptic sequences not recognized as “self” when displayed by MHC1 on the cell surface.

In their search for matching peptide antigens, activated T cells permeate all tissues, including the central nervous system (CNS). Cytotoxic T cells initially primed in regional tumor-draining lymph nodes are unlikely to encounter mutated or aberrantly cleaved peptides in surveilling the resting nervous system. However, the release of interferon-γ remotely, in the course of systemic infection or traumatic injury, could

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**FIGURE 3.** A. Neurologic autoimmune attack by cytotoxic T cells (CTLs) targeting intracellular-derived antigens. Antigenic peptides arising from neural cytoplasmic and nuclear proteins degraded by the proteasome are transported to the endoplasmic reticulum (ER) for processing and loading onto major histocompatibility complex class I (MHC1) molecules. Inflammatory cytokines promote translocation of MHC1-peptide complexes to the plasma membrane for interaction with antigen-specific CTLs. B. Neurologic autoimmune attack by autoantibodies targeting plasma membrane antigens. Binding of IgG to the extracellular domain of a neural plasma membrane protein may lead to the antigen’s internalization or functional blockade or to killing or damage of the target cell by antibody-dependent cellular cytotoxicity (ADCC) or via complement activation. Target membrane lysis or opsonization and phagocytosis ensue. TAP = transporter of antigenic peptides.
up-regulate display of immunoproteosome-processed peptide fragments complexed to MHC1 in the nervous system.1,7

Neuronal, glial, and muscle synaptic membranes are highly vulnerable to interaction with IgGs specific for extracellular domain epitopes of ion channels, water channels, neurotransmitter receptors, and neural adhesion proteins.6,7 IgGs of high affinity and appropriate class are potentially pathogenic (Figure 3B). Some can initiate complement activation (with or without membrane lysis), antigen internalization, functional blockade, opsonization/phagocytosis, or antibody-dependent cell-mediated cytotoxicity. Because they are functionally monovalent, IgG4 antibodies are incapable of activating complement, internalizing antigen, opsonizing membranes, or mediating antibody-dependent cell-mediated cytotoxicity. However, they can dissociate interacting multimeric protein complexes.6,7 Myasthenia gravis, a synaptic neuromuscular transmission disorder, exemplifies multiple pathogenic mechanisms. Muscle acetylcholine receptor–specific-IgGs (the commonest effector, largely IgG1 and IgG3 subclasses) reduce the density of neurotransmitter receptors in the postsynaptic membrane of skeletal muscle by antigen internalization or by complement-dependent lysis (terminal membrane attack complex) or opsonization (C3b-promoted phagocytosis).16 The effector autoantibody in a small minority of cases is muscle-specific tyrosine kinase (MUSK)-IgG (largely IgG4). It disrupts the muscle’s postsynaptic membrane signaling by interfering with interactions between AChR-associated proteins.16,17 Animal models have demonstrated the pathogenic potential of other synaptic autoantibodies. For example, active immunization with the neuronal nicotinic AChR α3 subunit induces pandysautonomia in rabbits and mild gastrointestinal hypomotility in mice.18,19 Intrathecal injection of IgG from patients with paraneoplastic cerebellar degeneration associated with metabotropic glutamate receptor (mGlur) type 1-IgG induces severe but reversible ataxia in mice.20,21

Additional theories have been proposed for the genesis of thymoma-associated autoimmunity. One relates to the role of the thymus in T-cell maturation.22 The tumorous human thymus is reported to have a higher lymphocyte proliferation rate than the normal adult thymus, as evidenced by more numerous T-cell receptor excision circles in newly circulating T cells. Recent thymic emigrants are presumed deficient in self-tolerance and prone to autoimmune activation.22 Another theory proposes that expression of the autoimmune regulator protein, a transcription factor promoting self-antigen expression in the thymic medulla, is reduced or altered in thymoma. Deficient negative selection of autoreactive T lymphocytes would result in loss of central tolerance.23

**Immune Checkpoint Inhibitor–Related Mechanisms**

Awareness of paraneoplastic neurologic autoimmunity has increased since the introduction of immune checkpoint inhibitor therapy to oncology practice. Monoclonal antibody–based therapies intercept early or late negative regulatory steps in T-cell immune responses.12 The rationale for therapeutic blockade of the cytotoxic T lymphocyte–associated antigen 4 (CTLA4) in cancer patients is to promote expansion of tumor-specific effector T-cell populations. Expansion of autoreactive T- and B-cell populations is an undesired outcome. The CTLA4 checkpoint protein translocates to the surface of a T cell activated by interaction of its antigen receptor with a peptide-MHC on an antigen-presenting cell in a tumor-draining lymph node. The CTLA4 down-regulates T-cell activation by out-competing the lower-affinity T-cell costimulatory receptor CD28 for the B7-1 or B7-2 ligand on an antigen-presenting cell.12,24

Therapeutic IgGs targeting the programmed cell death 1 (PD1) protein, or its ligand (PDL1), are a second class of immune checkpoint inhibitors. These agents intercept effector T-cell responses at the tumor level. About one-half of human cancers express PDL1. Interaction of PDL1 with PD1 protein on activated tumor-infiltrating...
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ALTERED IMMUNE RESPONSES TO TUMORS CAN AUGMENT AN AUTOIMMUNE RESPONSE THAT IS DRIVEN BY CANCER ANTIGENS.

In addition to the mechanisms proposed previously, other plausible hypotheses have been suggested for the induction of neurologic complications in patients treated with immune checkpoint inhibitors. For example, potentiation of a preexisting non–cancer-related immune response could explain the exacerbation of multiple sclerosis in patients treated with checkpoint inhibitors. In a mouse model of experimental autoimmune encephalomyelitis induced by myelin oligodendrocyte glycoprotein peptide, administration of IgG blocking the PD1/PDL1 pathway exacerbated experimental autoimmune encephalomyelitis and enhanced antigen-specific T-cell activation and expansion and production of cytokines and myelin oligodendrocyte glycoprotein (MOG) -IgG. Off-target tissue cytotoxicity of the checkpoint inhibitor IgG per se is recognized to cause neurologic impairment independent of the antitumor immune response. For example, direct binding of anti-CTLA4 -IgG has been implicated in the pathogenesis of hypophysitis, a relatively common adverse effect of CTLA4 blockade therapy. When given to healthy mice, anti-CTLA4-IgG induced hypophysitis with lymphocytic infiltration and pituitary autoantibodies in serum. Normal mouse pituitary glands were shown to express CTLA4, and products of complement activation were deposited at those sites in mice receiving anti-CTLA4 -IgG.
CLINICAL-SEROLOGIC CORRELATIONS

Spontaneous autoimmune neurologic disorders are recognized most commonly with SCLC, thymoma, gynecologic cancers (ovarian carcinoma or teratoma, endometrial, fallopian tubal, or breast carcinoma), seminoma, and hematologic malignancies. Although spontaneous autoimmune neurologic associations are relatively infrequent with melanoma, these disorders are encountered more frequently with the use of immune checkpoint inhibitor therapy. Anticipating that the use of checkpoint inhibitors as first-line therapy will increase the number of autoimmune neurologic complications seen by oncologists, we will first discuss the most common spontaneous presentations of neurologic autoimmunity according to cancer type. Then we will discuss neurologic complications that have been reported to date in the context of checkpoint inhibitor therapy. The Table summarizes well-characterized neural autoantibodies according to the cellular and subcellular location of the autoantigen and the associated oncological and neurologic manifestations.

Small Cell Lung Cancer

Small cell lung carcinoma is notorious for having remote systemic manifestations beyond those attributable to metastatic, nutritional, infectious, or therapeutic complications. Metabolic paraneoplastic syndromes reflect a tumor’s secretion of peptides (e.g., parathyroid hormone–related protein causing hypercalcemia). This tumor’s neuroendocrine phenotype reflects an up-regulation of neuronal transcription factors, attributed to clonally reduced expression of the neuron-restrictive silencer factor. Resultant neuropeptide secretion and expression of neurotransmitter-releasing and signaling proteins, such as voltage-gated and ligand-gated plasma membrane channels, promote SCLC survival and growth.

One or more SCLC-related autoantibodies are demonstrable in the serum of 90% of patients with SCLC who present with neurologic impairment unrelated to metastases and in 40% of SCLC patients without any evident neurologic disorder. Multiple neural-specific IgGs and paraneoplastic disorders often coexist in a single patient. The SCLC-related IgGs identified most commonly are specific for SOX transcription factor proteins (SOX1 and SOX2), Hu proteins (antineuronal nuclear autoantibody [ANNA] type 1), voltage-gated calcium channels (VGCCs; P/Q type and N type), collapsin response-mediator protein 5 (CRMP5), metabotropic γ-aminobutyric acid (GABA) type B receptors, amphiphysin, and microtubule-associated protein 1B (antigen of Purkinje cell cytoplasmic autoantibody [PCA] type 2).

Antineuronal nuclear autoantibody type 1-IgG is a biomarker of several classically recognized SCLC-associated syndromes, such as...
sensory neuronopathy, limbic encephalitis, and gastrointestinal dysmotility.37,39 CD8+ T cells specific for peptides derived from the Hu protein (the antigen of ANNA1 IgG) have been demonstrated in peripheral blood of ANNA1-IgG-seropositive SCLC patients.40 An IgG targeting P/Q-type VGCCs is implicated as the cause of neuromuscular weakness in the Lambert-Eaton myasthenic syndrome.31 Cerebellar ataxia, with and without Lambert-Eaton myasthenic syndrome, can coexist.32 Coexisting SOX1-IgG predicts a paraneoplastic etiology for Lambert-Eaton myasthenic syndrome.9

Small cell lung carcinoma—related limbic encephalitis may be accompanied by other autoantibodies, such as GABABR-IgG (seizures are prominent) and AMPAR-IgG (Figure 4).32,43 Neurologic accompaniments syndromic of the CRMP5-IgG include chorea, transverse myelitis, optic neuritis/retinitis, other cranial neuropathies, and plexoradiculoneuropathies (Figure 4).2 An autoantibody specific for neuronal intermediate filament light chain has recently been described in association with SCLC and other neuroendocrine tumors, particularly Merkel cell carcinoma. The principal neurologic presentation is cerebellar ataxia, but encephalopathy, myelopathy, and peripheral nerve involvement were reported.44 Purkinje cell cytoplasmic antibody type 2-IgG is another SCLC biomarker with similar neurologic associations. Its antigen is the microtubule-associated protein 1B.38

Thymic Epithelial Tumors
Thymoma is highly associated with neurologic, rheumatologic, hematologic, endocrine, and cutaneous autoimmune disorders.45,46 Remarkably, myasthenia gravis is predicted to develop in 25% of all patients with thymoma.45,46 Neuromuscular transmission is critically impaired in myasthenia gravis by IgG targeting skeletal muscle nicotinic AChRs. However, 33% of patients with thymoma are AChR-IgG seropositive without clinically evident myasthenia gravis or other neurologic problem.45 Striational autoantibodies (specific for cytoplasmic contractile proteins of skeletal and cardiac muscle) are found in 76% of patients with paraneoplastic myasthenia gravis and are quite common, in low titer, in patients with nonneurologic autoimmune diseases or cancer.46,47

Other neurologic manifestations of thymoma include dysautonomia (gastrointestinal dysmotility occurs in half of those cases), encephalitis (limbic or cortical), and peripheral nerve hyperexcitability (neuromyotonia), which are classic signs of Kv1 voltage-gated potassium channel complex autoimmunity).45,46,48 Hyperexcitability involving the central, peripheral, and autonomic nervous systems is known as Morvan syndrome. Other synaptic autoantibodies that commonly accompany thymoma (with and without neurologic manifestations) are specific for ganglionic-type (z3) nicotinic AChR (dysautonomia) and AMPAR (limbic/cortical encephalitis). Less frequent specificities include aquaporin-4 (neuromyelitis optica spectrum disorders), glycine receptor (rigidity, muscle spasms, brain stem signs, stiff-person syndrome or exaggerated startle), and GABABAR-IgG (encephalitis and seizures).46,47 Autoantibodies of intracellular specificity sometimes accompany thymoma. These include CRMP5-IgG (myelitis, optic neuritis, other cranial neuropathy, encephalopathy, chorea, or radiculoneuropathy), glutamic acid decarboxylase 65(GAD65)-IgG (stiff-man phenomena, autoimmune epilepsy, and cerebellar ataxia) and, rarely, ANNA1-IgG.46

Gynecologic Tumors
Patients seropositive for PCA 1 (anti-Yo/anti-cdr2) are female in 99% of cases. Purkinje cell cytoplasmic autoantibody type 1 IgG predicts a mullerian adenocarcinoma (ovarian, fallopian tubal, endometrial, or serous surface papillary) and less commonly ductal breast carcinoma.7 Gastrointestinal adenocarcinomas are usually found in the 1% of male cases.49 The most common presentation of PCA1-IgG—positive patients is cerebellar ataxia, and this is one of the best-characterized paraneoplastic CNS disorders mediated by tumor-specific CD8+ T cells (Figure 4).3 Seropositivity correlates with limited metastasis.5 The blood of
seropositive patients contains expanded populations of cytotoxic and memory T cells that are cdr2 peptide specific and MHC1 restricted. Autoantibodies specific for GTase regulator associated with focal adhesion kinase 1(GRAF1) and carbonic anhydrase-related protein (CARP) VIII have been reported in rare cases of ovarian cancer—related cerebellar ataxia.

Antineuronal nuclear autoantibody type 2- IgG and amphiphysin- IgG predict breast carcinoma. ANNA2 -IgG is specific for NOVA1 and NOVA2 RNA-binding proteins and amphiphysin IgG for a protein involved in retrieval of neurotransmitter-vesicle membranes from the plasma membrane following exocytosis. Both of these autoantibodies predict SCLC in men and, less commonly, women (with smoking history). Syndromic manifestations of ANNA2 -IgG involve opsoclonus-myoclonus syndrome, jaw dystonia, and laryngospasm. Patients with breast carcinoma who are seropositive for amphiphysin IgG frequently have stiff-man—type manifestations, whereas encephalopathy, myelopathy, and peripheral neuropathy are more typical presentations with lung cancer. Synaptic IgG specificities encountered with breast carcinoma include N-type or P/Q-type VGCC, neuronal and muscle AChRs, AMPAR, and aquaporin-4 water channel.

N-methyl-D-aspartate receptor (NMDAR) autoantibody was first recognized as a serologic accompaniment of ovarian teratoma in 2007. Approximately 50% of young female NMDAR-IgG—seropositive patients have an ovarian teratoma. Seropositive patients present with stereotypic psychiatric symptoms, memory loss, altered consciousness, seizures, abnormal movements, and central hypoventilation. Autoimmune NMDAR encephalopathy usually responds favorably to immunotherapy and tumor removal. Ovarian teratomas of seropositive patients contain morphologically atypical neural elements not found in control ovarian teratomas. The pathogenic potential of NMDAR-IgG was demonstrated in vitro by its binding to NMDARs on live hippocampal neurons, with subsequent cross-linking and internalization. Infusion of patients’ cerebrospinal fluid containing NMDAR- IgG into the ventricular system of live mice causes progressive memory deficits.

If NMDAR- IgG is accompanied by 2 astrocyte-specific autoantibodies, aquaporin-4- IgG and glial fibrillary acidic protein (GFAP)- IgG, the positive predictive value for teratoma is 70%. Glial fibrillary acidic protein IgG is associated with numerous cancers. Its neurologic correlate is a relapsing autoimmune meningoencephalomyelitis with inflammatory spinal fluid, characteristic magnetic resonance imaging findings, and remarkable corticosteroid responsiveness. As predicted for cytoplasmic protein—specific autoantibody positivity, the biopsied leptomeninges of a GFAP- IgG—seropositive patient contained mononuclear cellular infiltration with an abundance of CD8+ T cells. Furthermore, CD8+ cytotoxic T cells specific for a GFAP peptide were demonstrated to be pathogenic in a transgenic mouse model of autoimmune meningoencephalitis.

Seminoma IgG specific for the nuclear Ma2 protein common to neuronal and testicular cells predicts seminoma in young men who present with diencephalic—brain stem encephalitis with or without cerebellar ataxia. The associated neuropathology shows mononuclear cell infiltrates (predominantly CD8+ T cells), and sometimes plasma cells, in the limbic region, brain stem, and cerebellum. The neurologic syndrome may respond favorably to tumor ablation. Dual seropositivity for the homologous Ma1 nuclear antigen is more frequent in women, predicts a worse neurologic outcome, and is associated with a variety of cancers and neurologic syndromes.

Hematologic Malignancies Peripheral neuropathies occurring with paraproteinemias are not proven to be antigen-specific autoimmune disorders. Examples of these neurologic disorders are POEMS syndrome (polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes),
myelin-associated glycoprotein IgM neuropathy, and amyloidosis associated with monoclonal gammopathy of unknown significance. On the other hand, cerebellar degeneration and limbic encephalitis occurring with hematologic malignancies are neural antigen–specific autoimmune disorders. Neuronal autoantigens identified to date include Delta/notch-like epidermal growth factor–related receptor (DNER, the antigen of PCA-Tr-IgG), mGluR1, and mGluR type 5. Unlike other paraneoplastic autoimmune neurologic disorders, symptoms and signs generally follow cancer diagnosis. A rare autoimmune synaptopathy targeting dipeptidyl-peptidase-like protein-6 (DPPX) has been associated with B-cell malignancies. This severe encephalopathy is generally responsive to early-initiated immunotherapy and is often accompanied by profound dysautonomia and gastrointestinal dysmotility.

**AUTOIMMUNE NEUROLOGIC DISORDERS IN THE ERA OF CHECKPOINT INHIBITOR CANCER IMMUNOTHERAPY**

Checkpoint inhibitor therapy is an emerging and underappreciated cause of neurologic autoimmunity. To date, these complications are thought to be relatively rare, with severe complications (greater than grade 3) estimated to be seen in less than 1% of cases. It is noteworthy that early reported neurologic complications, fatal in some cases, have arisen in the context of cancers not commonly associated with spontaneous neurologic autoimmunity, such as melanoma. Agents targeting both PD1/PDL1 and CTLA4 pathways, singly and in combination, have been implicated, with symptoms reported early after initiating treatment (in the first days or weeks) and sometimes following treatment cessation. Hypophysitis, a neuroendocrine complication, is encountered most often in patients treated with CTLA4-blocking IgG who present with headache, cognitive difficulties, and deficiencies of anterior pituitary hormones, particularly corticotropin and thyrotropin; central diabetes insipidus has also been reported. Long-term hormone replacement therapy may be required, even when treated with corticosteroids.

Aseptic meningitis as a complication is often responsive to corticosteroids. Encephalitis that is also often immunotherapy responsive has been described in several cases. Most of the cases are neural autoantibody negative, but there have been descriptions of NMDAR-IgG, voltage-gated potassium channel complex (contactin-associated protein 2)-IgG, ANNA1, and Ma2-IgG–seropositive cases. In addition, neuronal intermediate filament light chain IgG has been seen in a patient with Merkel cell carcinoma and cerebellar ataxia. Cases of posterior reversible encephalopathy syndrome have also been reported. Aggravation of CNS demyelinating disease was seen in patients treated with immune checkpoint inhibitors who previously had sustained clinical remission. Transformation of a previous radiologically isolated syndrome to clinical multiple sclerosis has also been documented, but patients were responsive to multiple sclerosis treatments. Myelitis, including longitudinally extensive myelitis, has also been described, and immunotherapeutic responses can be favorable.

Peripheral nerve involvement has been reported in less than 3% of patients receiving checkpoint inhibitor therapy for cancer. In some patients, manifestations have been compatible with demyelinating polyradiculoneuropathies (Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy). In contrast to idiopathic cases, cerebrospinal fluid pleocytosis can be encountered. Meningoradiculonuritis, plexitis, and enteric and cranial neuropathies also have been reported. Myasthenia gravis has been reported as a potentially fatal complication. Among more than 9000 patients receiving a PD1 inhibitor (nivolumab), 12 had development of myasthenia gravis. Bulbar and respiratory manifestations were more common than in idiopathic myasthenia gravis, and
myocarditis was a common accompani-

ment. Reported cases of myositis often resemble clinical manifestations of myas-

thenia gravis. Symptoms are sometimes

resemble clinical manifestations of myas-

mune response. The response triggered by

Paraneoplastic neurologic autoimmunity re-

CONCLUSION

Complications.29,30,81,83 Reintroduction of

apy was stopped early because of neurologic

some cases when checkpoint inhibitor ther-

apy is based on expert opinion and depends on the severity and type of neuro-

logic manifestations.86 A watchful waiting

approach might be elected for patients who

have only minor symptoms. In more severe
cases, checkpoint inhibitor agents can be

suspended or permanently discontinued.86

Corticosteroids are considered first-line ther-

ey, even when an alternative approach

would be preferred in an idiopathic setting

(eg, cases of Guillain-Barré syndrome).

Neurologic manifestations usually improve

with immunotherapy and discontinuation

of checkpoint inhibitor therapy.29,30,81,83

Cancer progression has been reported in

some cases when checkpoint inhibitor ther-

apy was stopped early because of neurologic

complications.29,30,81,83 Reintroduction of

immune checkpoint inhibitor should be dis-

cussed on a case-by-case basis, assessing the

risk and benefits of other options. It remains

to be determined whether testing a patient’s

serum autoantibody profile before

commencing checkpoint inhibitor treatment

will predict the likelihood of autoimmune

neurologic complications. In a prospective

serologic study of patients with thymoma

who subsequently received a PDL1 inhibitor

IgG, myositis developed only in those who

had preexisting muscle AChR- IgG and not

in patients who were seronegative.10

CONCLUSION

Paraneoplastic neurologic autoimmunity re-

flects an effective multifaceted antitumor im-

mune response. The response triggered by

neoadigens expressed in tumors attacks

self-antigens in the nervous system. Effector

T cells and IgG products of this response

target both mutant and native forms of

self-proteins. Recognition that a neurologic

presentation is paraneoplastic allows earlier
diagnosis of a new or recurrent cancer.

Neurologic presentations are varied and

involve multiple levels of the nervous sys-

tem. This largely unappreciated aspect of tu-

mor immunology is highly pertinent to

contemporary oncological practice in view

of the anticipated increase in frequency of

neurologic autoimmunity with wider use of

immune checkpoint inhibitors as first-line
cancer therapy.

Abbreviations and Acronyms: AChR = acetylcholine re-

ceptor; AMPAR = a-amino-3-hydroxy-5-methyl-4-is-
xazolopropionic acid; ANNA = antineuronal nuclear

autoantibody; CARP VIII = carbonic anhydrase VIII; CNS =
central nervous system; Caspr2 = contactin-associated

protein-2; CRMP5 = collapsin response-mediator protein 5;

CTLA4 = cytotoxic T lymphocyte—associated antigen 4;

DNER = δ Notch-like epidermal growth factor—related

receptor; DPPX = dipeptidyl-peptidase—like protein-6;

GABA = γ-aminobutyric acid; GFAP = glial fibrillary acidic

protein; HA = hemagglutinin antigen; LGI1 = leucine-rich,
glioma-inactivated 1 protein; mGlUR = metabotropic

glutamate receptor; MHC1 = major histocompatibility

class I; MHC2 = major histocompatibility complex
class II; NMDAR = N-methyl-D-aspartate receptor; PCA =

Purkinje cell cytoplasmic autoantibody; PD1 = programmed
cell death 1; PDL1 = programmed cell death ligand 1; SCLC =

small cell lung carcinoma; VGCC = voltage-gated calcium

channel

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