Review Article

Neurologic Complications of Melanoma

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Neurologic complications are common in patients with melanoma and are often associated with a poor prognosis. In an era with new, effective treatments, patients are living longer, and this has resulted in an increase in complications of both the disease and the therapy. A multidisciplinary approach to neurologic complications in patients with melanoma, with involvement from medical oncology, neuro-oncology, radiation oncology, and often neurosurgery, is necessary. In this review, neurologic complications of melanoma, including clinical implications and treatment strategies, are described. ***Cancer* 2020;126:477-486**. *© 2019 American Cancer Society*.

KEYWORDS: melanoma, neurologic, neuro-oncology.

INTRODUCTION

The field of neuro-oncology within melanoma is broad and ranges from direct extension of malignancy, including perineural invasion, intraparenchymal brain metastases, leptomeningeal spread, and paraneoplastic syndromes, to sequelae of treatment, such as immune-related adverse effects (irAEs) from immune checkpoint inhibitors and necrosis from radiation therapy. Research has advanced the understanding of each of these unique complications; however, many questions remain unanswered. Because of the distinct presentations of each potential neurologic complication, a multidisciplinary team promoting different therapeutic approaches should be considered.

MELANOMA-RELATED NEUROLOGIC COMPLICATIONS

Perineural Invasion

Perineural tumor spread is a well-documented mechanism of metastasis in all head and neck malignancies. Melanoma demonstrating neurotropism typically arises from a primary on the head and neck region with desmoplastic histology and is associated with increased local recurrence and decreased disease-free survival.[1-5] Cranial nerves (trigeminal and facial) are most commonly affected, although nerve invasion of the brachial plexus has been reported as well.[6-8]

Forty percent of perineural invasion in melanoma is asymptomatic; however, cranial nerve palsies, paresthesias, pain, and neuropathies can occur. In asymptomatic cases, the diagnosis is often made by pathologic examination after surgery or on the basis of radiologic findings in more advanced cases. Imaging demonstrates destruction of fat planes around cranial nerve exit points and along the nerve routes.[2,9] Magnetic resonance imaging (MRI) is the imaging method of choice for detecting perineural invasion because it allows for the entire course of the involved cranial nerve to be evaluated.

Historically, before the introduction of effective immune checkpoint inhibitors or targeted therapies, treatment of perineural invasion in melanoma focused on surgery, if feasible, followed by radiation with or without adjuvant systemic therapy if appropriate. A number of studies have investigated the role of radiation in improving local control in perineural invasion. One of the earliest studies looked at desmoplastic neurotropic melanoma only.[10] Patients with poor prognostic features (Clark level of invasion and narrow margins) received radiation after surgery. The local recurrence rate was 7.4% at a median follow-up of 40.5 months, whereas it was 5.9% for a cohort receiving surgery alone; this confirmed a favorable approach for local control with the addition of adjuvant radiotherapy. Similar subsequent studies compared local recurrence rates with and without radiation, and they typically favored radiation for those patients with more risk factors.[11,12] This was particularly significant before the Food and Drug Administration approval of systemic adjuvant therapies for both BRAF-mutated and BRAF wild-type melanoma. Now, with the options of targeted therapies for BRAF-mutated patients and immune checkpoint inhibitors for BRAF wild-type

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or BRAF-mutated patients, the postsurgical treatment paradigm has shifted. In these patients, adjuvant systemic therapy can be given after radiation, or radiation can be reserved for local recurrences. Multidisciplinary discussions of individual cases with perineural invasion are now helpful when one is deciding whether the benefits of radiation outweigh the risks in patients who can start adjuvant immune checkpoint inhibitors or targeted therapy for symptomatic relief first, and then radiation can be reserved for refractory cases.

Leptomeningeal Metastases

Leptomeningeal disease (LMD) occurs more frequently in patients with melanoma (6%-18%) in comparison with many other cancers.[13,14] The full pathogenesis is not completely understood; however, involvement of leptomeninges and the subarachnoid space is thought to occur through direct extension from brain parenchyma, dura, bone, or hematologic spread and potentially via perineural extension.[15] Nonobstructive hydrocephalus is a common manifestation of LMD due to microscopic obstruction of villi with malignant cells, which can impair cerebrospinal fluid (CSF) resorption and obstruct flow and thus lead to increased intracranial pressure. The prognosis for patients with LMD, regardless of malignancy, is poor with a median overall survival (OS) of 4 to 6 weeks without treatment.[15,16] However, a recent study of 178 patients with LMD from melanoma predicted improved OS for a subset of patients.[17] The Eastern Cooperative Oncology Group performance status was a significant predictor of survival, with a decline in the performance status correlating with a decline in survival. Similarly, neurologic symptoms correlated with a poorer prognosis. However, patients who received at least 1 treatment for LMD (intrathecal [IT] therapy or radiation therapy) had improved survival in comparison with patients who did not receive treatment.

LMD is typically initially detected with brain MRI, which has a sensitivity of 70% and a specificity of 77% to 100%.[18-20] MRI findings include sulcal or cranial nerve enhancement, sometimes with adjacent parenchymal edema or hydrocephalus (Fig. 1). Because of the propensity for metastases to the brain in patients with melanoma, imaging with MRI will often detect LMD before neurologic symptoms appear. Asymptomatic patients are treated similarly to symptomatic patients because of the known poor prognosis for this population of patients. Once patients have neurologic symptoms and/or MRI findings suggesting LMD, a lumbar puncture is not necessary to make the diagnosis, although

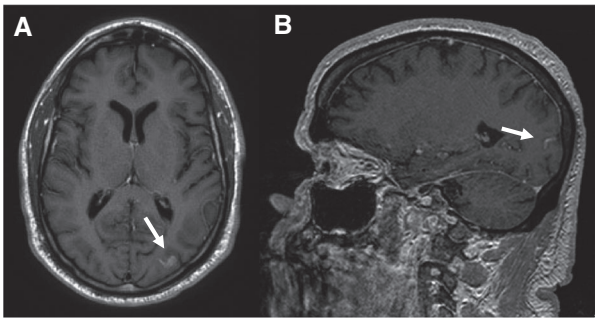

Figure 1. Leptomeningeal metastasis. Postgadolinium T1-weighted (A) axial and (B) sagittal magnetic resonance imaging sequences demonstrate sulcal enhancement in the left occipital lobe suggestive of leptomeningeal metastasis (arrow).

it is often required for any patients pursuing a clinical trial. If a lumbar puncture is performed, cytology is positive in >90% of patients with suspected LMD if there is adequate CSF (at least 10 mL) with immediate processing.[16,21] Specificity is >95% if there are 3 high-volume lumbar punctures, although false-negative results can occur if the sample is not large enough, it is not processed quickly enough, or there are concurrent infectious or inflammatory conditions.

Analysis typically reveals mild pleocytosis, elevated protein levels, and hypoglycorrhachia. Cytology with malignant cells confirms the diagnosis.

In the era before immune checkpoint inhibitors and targeted therapies, various combinations of IT chemotherapy, systemic therapy, and best supportive care showed a modest benefit with the combination of IT chemotherapy and systemic therapy.[22] IT interferon-α-2b showed minimal activity.[23,24] IT interleukin 2 alone and in combination with tumor-infiltrating lymphocytes has also been studied[25-28]; however, radiation remained the standard of care because of a lack of clinical benefit with more invasive therapies and the small numbers in studies and case reports. On the basis of retrospective studies of LMD in breast and lung cancer, radiation does not prolong survival but may improve symptoms.[29,30]

Initial clinical trials of BRAF inhibitors and BRAF/MEK inhibitor combinations excluded patients with LMD. However, case reports of patients with LMD from BRAF V600E–mutated melanoma have described responses to BRAF inhibitors and suggested the potential of a targeted therapeutic approach.[31-34] One retrospective case series reported a median OS of 22 weeks for patients who received BRAF inhibitors and ipilimumab.[35] Immunotherapy clinical trials also excluded patients

TABLE 1. Clinical Trials That Are Active and/or Recruiting Patients With Leptomeningeal Disease From Melanoma

Trial Title	NCT Designation	Status
Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization in Patients With Melanoma	0338377	Recruiting
Intravenous and Intrathecal Nivolumab in Treating Patients With Leptomeningeal Disease	03025256	Recruiting
Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients With Central Nervous System Cancer or Leptomeningeal Cancer	00445965	Active, not yet recruiting
Ipilimumab and Nivolumab in Leptomeningeal Metastases	02939300	Recruiting
Concurrent Intrathecal-Pemetrexed and Involved-Field Radiotherapy for Leptomeningeal Metastasis From Solid Tumors	03507244	Active, not yet recruiting
Study of Proton Radiation to the Brain and Spinal Cord for Patients With Leptomeningeal Metastases	03520504	Recruiting
Avelumab With Radiotherapy in Patients With Leptomeningeal Disease	03719768	Recruiting
Pembrolizumab in Patients With Leptomeningeal Disease	03091478	Recruiting

Abbreviation: NCT, National Clinical Trial.

with LMD. A retrospective study from France analyzed 28 patients with melanoma LMD. None of the patients were treated with radiation. Systemic treatments included chemotherapy (n = 18), BRAF inhibitors (n = 9), MEK inhibitors (n = 3), and immunotherapy (n = 4). Ten patients received more than 1 line of therapy, and the median OS was 3.1 months for the whole cohort. Another case series published in 2018 described 14 patients with LMD from melanoma.[36] Thirteen patients received radiation, 9 patients received immunotherapy (anti-PD1, anti-CTLA4, or both), and 4 patients received targeted therapy. Interestingly, 7 patients developed LMD while they were on targeted therapy. The patients who received targeted therapy had a median OS of 7.2 months. The patients who received anti-PD1 therapy had a median OS of 7.1 months. The study confirms a clear OS benefit with a multimodality approach to patients with LMD, with both BRAF/MEK inhibitors and immunotherapy showing promise.

The ABC phase 2 trial of a combination of ipilimumab plus nivolumab versus nivolumab in patients with brain metastases included a cohort of patients with LMD. The results suggest that combination therapy has a better response rate in this population.[37] Multiple immunotherapy or cell therapy–based clinical trials are currently active and recruiting patients (Table 1).

Incorporating patients with LMD into clinical trials as well as designing protocols focused on this population is critical because this will allow for guided treatment options and translational science progress. Research exploring future directions for patients with LMD is focusing on the analysis of CSF to include the detection of cell-free DNA, cell-tumor DNA, and circulating tumor cells, single-cell sequencing, and whole-exome sequencing. CSF tumor markers have a low sensitivity and specificity, and the results may have wide variability due to different assay techniques. However, these data may be useful in certain malignancies with known tumor makers (eg, carcinoembryonic antigen in adenocarcinomas, α-fetoprotein in hepatocellular and testicular carcinomas, and β-human chorionic gonadotropin in choriocarcinomas and testicular carcinomas). Tumor markers used in this context may be able to predict responses to therapy or detect minimal residual disease. Finally, genomic profiling of CSF may be an opportunity for identifying potentially targetable mutations and directing treatment for this difficult disease.[38-41]

Brain Metastases

Perhaps the most common neurologic complication of melanoma results from brain metastases with an incidence of 50% (and an additional 40% noted on autopsy); this makes melanoma the malignancy with the highest frequency of central nervous system metastases.[42-44] Melanoma can metastasize to any part of the brain, with the cerebrum, cerebellum, and pons being the most common locations. There are multiple theories describing the high propensity of melanoma for the brain. Most likely, metastatic melanocytes cross the blood-brain barrier while seeking soluble growth factors and cytokines, which are produced in the brain.[45] However, the complex signaling that occurs between brain metastases and their microenvironment during the process of metastasis is speculated but incompletely understood.[46-49] There are data suggesting that brain metastases often harbor oncogenic drivers not detected in the primary tumors or extracranial sites.[50-52]

Focal neurologic symptoms are noted in approximately 20% to 40% of patients with melanoma brain metastases (MBMs) according to the location of the brain involved with metastases.[53-55] Approximately 40% to 60% of MBMs have intratumoral hemorrhaging, which

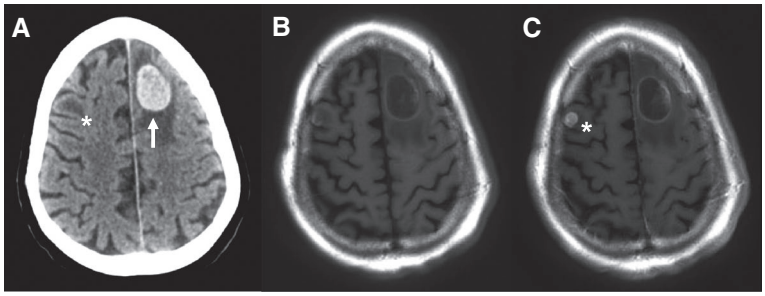

Figure 2. Hemorrhagic metastasis. (A) A noncontrast head computed tomography scan reveals a hyperdense, acute hemorrhage in the left frontal lobe with surrounding hypodensity representing edema (solid arrow). There is also hypodensity in the right frontal lobe suggestive of a second, nonhemorrhagic lesion (asterisk). (B) Pregadolinium T1-weighted sequences show a cystic-appearing lesion in the left frontal lobe that is T1-hypointense; it represents an acute intralesional hemorrhage. (C) Postgadolinium T1-weighted sequences reveal minimal enhancement around the hemorrhagic left frontal lesion and confirm an enhancing lesion in the right frontal lobe (asterisk). Resection of the hemorrhagic left frontal lesion revealed metastatic melanoma.

can lead to the development of acute focal neurologic symptoms.[56] An acute intratumoral hemorrhage may have intrinsic T1 precontrast hyperintensity on brain MRI and appears hyperdense on noncontrast head computed tomography (Fig. 2). MBM typically results in significant surrounding edema, which is noted on brain MRI as T2/fluid-attenuated inversion recovery hyperintensity. Large MBMs or several smaller lesions with associated peritumoral edema can lead to an increase in intracranial pressure and herniation. Focal seizures can often be the presenting symptom of patients with MBMs.[57]

Steroids play a pivotal role in the management and control of peritumoral edema.[58,59] Dexamethasone is the most commonly used steroid in brain metastases, although it is often used for other malignancy-associated conditions such as post-IT therapy or therapy-induced meningitis. Clinical practice guidelines recommending steroids to control edema in brain metastases have been published by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), the American Society of Clinical Oncology, and the Society of Neuro-Oncology. Dexamethasone at 4 to 8 mg/d as a single dose or 2 divided doses is typically the initial recommendation, and this can be increased to 16 mg/d in patients with severe neurologic symptoms. Because of the long list of adverse effects associated with long-term steroid use, the general recommendation is to decrease the steroids to the lowest tolerated dose as soon as possible. Bevacizumab can occasionally be used in the management of edema or radiation necrosis.[60-63]

Prophylactic antiepileptics are not routinely recommended for patients with MBMs unless seizures have been reported or witnessed.[64] The choice of anticonvulsant is based on the toxicity profile and drug-to-drug interactions.

The treatment paradigm for MBMs is changing as the landscape of available therapies for this malignancy evolves. A multidisciplinary approach to the treatment of MBMs is crucial. Surgery, radiation therapy, targeted therapies, and immune checkpoint inhibitors can be used alone or in various combinations. The nuances of the timing, feasibility, and alleviation of symptom management require a personalized, individual approach. With 4 potential options for treatment and numerous combinations, the prognosis of MBMs is improving dramatically. In addition, response assessment is being addressed by the Response Assessment in Neuro-Oncology (RANO) working group. The RANO working group has further defined criteria for brain metastases (RANO-BM) by differentiating intracranial and extracranial measurements for response.[65,66] In the era of immunotherapy, the RANO group has also published immune RANO criteria (iRANO) to address the nuances of measuring responses in patients receiving immunotherapy.

Surgery is the treatment of choice for solitary, large, symptomatic MBMs involving resectable cortical locations. Surgery can lead to significant and rapid symptom relief and allow for a faster steroid taper. Radiation therapy to the surgical cavity is typically recommended to decrease the incidence of local recurrence.[67] Stereotactic radiosurgery (SRS) and Gamma Knife are increasingly being used for the management of nonsurgical MBM concurrently with systemic therapy.[68-71] Whole-brain radiation therapy (WBRT) was historically the standard of care for patients with multiple brain metastases from melanoma. However, WBRT is much less commonly used in the modern era because of its poor rates and durability of response in combination with a high risk of fatigue and neurocognitive sequelae. As described later, WBRT has been largely supplanted by systemic therapy

TABLE 2. Ongoing Drug Therapy Clinical Trials for Patients With Brain Metastases From Melanoma

Clinical Trials With an Immune Checkpoint Inhibitor Backbone for Patients With Brain Metastases From Melanoma	NCT Designation	Status
Optune Device—TT Field Plus Nivolumab and Ipilimumab for Melanoma With Brain Metastasis	03903640	Active, not yet recruiting
Evaluation of Safety and Efficacy of Patients With Four and More Symptomatic Brain Metastases of Melanoma	03728465	Active, recruiting
Anti-PD 1 Brain Collaboration for Patients With Melanoma Brain Metastases	02374242	Active, not recruiting yet
A Study of Fotemustine (FTM) vs FTM and Ipilimumab (IPI) or IPI and Nivolumab in Melanoma Brain Metastasis	02460068	Active, recruiting
Pembrolizumab and Stereotactic Radiosurgery for Melanoma or Non–Small Cell Lung Cancer Brain Metastases	02858869	Active, recruiting
PD-L1 PET Imaging in Melanoma Patients	03520634	Active, recruiting
Melanoma Metastasized to the Brain and Steroids	03563729	Active, recruiting
Anti-PD 1 Brain Collaboration + Radiotherapy (ABC-X Study)	03340129	Active, not yet recruiting
Low Dose Ipilimumab With Pembrolizumab in Treating Patients With Melanoma That Has Spread to the Brain	03873818	Active, recruiting
SRS and Nivolumab in Treating Patients With Newly Diagnosed Melanoma Metastases in the Brain or Spine	02716948	Active, recruiting
Pembrolizumab Plus Bevacizumab for Treatment of Brain Metastases in Metastatic Melanoma or Non–Small Cell Lung Cancer	02681549	Active, recruiting
Study of Bevacizumab in Combination With Atezolizumab in Patients With Untreated Melanoma Brain Metastases	03175432	Active, recruiting
Clinical Trials With a Targeted Therapy Backbone for Patients With Brain Metastases From Melanoma	**NCT Designation**	**Status**
Concurrent Dabrafenib and Trametinib With Stereotactic Radiation in Patients With BRAF Mutation–Positive Malignant Melanoma and Brain Metastases	02974803	Active, recruiting
An Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-Dose and a High-Dose Regimen in Patients With BRAFV600-Mutant Melanoma Brain Metastasis	03911869	Active, not yet recruiting
[18F] Dabrafenib Molecular Imaging in Melanoma Brain Metastasis	02700763	Active, recruiting
Vemurafenib Plus Cobimetinib After Radiosurgery in Patients With BRAF-Mutant Melanoma Brain Metastases	03430947	Active, recruiting
Buparlisib in Melanoma Patients Suffering From Brain Metastases (BUMPER)	02452294	Active, recruiting
Encorafenib and Binimetinib Before Local Treatment in Patients With BRAF Mutant Melanoma Metastatic to the Brain	03898908	Active, not yet recruiting
E6201 for the Treatment of Metastatic Melanoma Central Nervous System Metastases (CNS)	03332589	Active, recruiting
JAK2 Inhibitor WP1066 in Treating Patients With Recurrent Malignant Glioma or Progressive Metastatic Melanoma in the Brain	01904123	Active, recruiting

Abbreviation: NCT, National Clinical Trial.

with intracranial penetration when diffuse disease, such as overwhelming brain metastases and/or leptomeningeal metastases, is present.

Finally, systemic therapies are being used more commonly for patients with MBMs. In patients with BRAF V600E–mutated melanoma, the combination of BRAF and MEK inhibitors is effective in brain metastases, with 56% to 59% showing an intracranial response (numbers vary with the prior treatment).[72,73] Patients with noncanonical BRAFV mutations also have intracranial responses, although the number is lower at 44%. There are currently 3 Food and Drug Administration–approved combinations for patients with BRAF-mutated melanoma (vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib).

Immune checkpoint inhibitors are the treatment of choice for patients without BRAF mutations. Specifically, the combination of ipilimumab plus nivolumab has a high intracranial response rate of 57% and, if tolerable, is the systemic standard treatment of choice for patients with MBMs.[37,74] Importantly, many ongoing clinical trials focusing on this population will give insight into the next steps for optimal therapy and timing (Table 2). Finally, adoptive cell therapy (ACT) is being explored in patients with MBMs. Early data for ACT with either tumor-infiltrating lymphocytes or T-cell receptor gene–transduced T cells and interleukin 2 were retrospectively gathered for patients with untreated brain metastases.[75] The results were promising and suggested that activated lymphocytes enter the central nervous system.[76] However, an expanded analysis with a larger population of patients and a comparison with patients without brain metastases showed that ACT alone is not sufficient for treating intracranial metastases.

Paraneoplastic Syndromes

Paraneoplastic syndromes are rare in melanoma, and only a few have been reported in the literature.

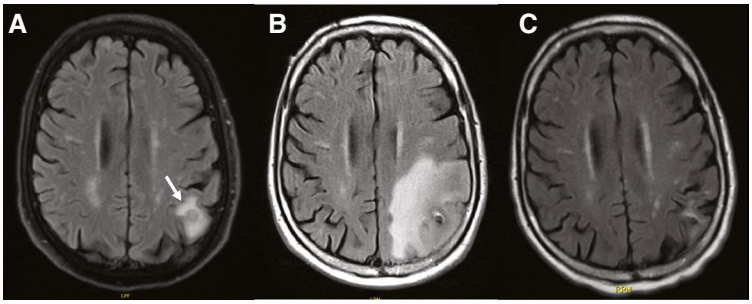

Figure 3. Radiation necrosis. (A) Axial T2/fluid-attenuated inversion recovery–weighted sequences on magnetic resonance imaging reveal a left parietal lesion with surrounding edema (arrow), which was treated with stereotactic radiosurgery. (B) Seven months later, the patient presented with a seizure, and imaging reveals significantly increased edema surrounding the treated left parietal lesion with internal blood products suggestive of radiation necrosis. (C) Repeat magnetic resonance imaging 6 months later demonstrates interval resolution of edema.

Melanoma-associated retinopathy is the most well-documented paraneoplastic syndrome associated with malignant melanoma.[77] Patients presenting with this condition have positive CV2 antibodies and rod-bipolar cell antibodies. Both antibodies have been postulated to affect rod cells while sparing cone cells and may be associated with a family history of autoimmune disorders.[78] These patients present with decreased night vision and peripheral visual field deficits. Paraneoplastic opsoclonus-myoclonus syndrome has also rarely been reported in the setting of melanoma, although it is more typically associated with small cell lung cancer. Interestingly, 3 of 4 cases reported in the literature were associated with mucosal melanoma.[79-82] Despite the rarity of paraneoplastic syndromes in melanoma, clinicians should be aware of this neurologic complication.

TREATMENT-RELATED NEUROLOGIC COMPLICATIONS

Radiation Necrosis

Multiple studies have shown that WBRT does not prolong OS and leads to neurocognitive defects, which are often irreversible.[83] In general, SRS provides 80% to 90% local control without the likelihood of cognitive impairment from WBRT.[84-86] However, radiation necrosis occurs in 5% to 10% per SRS target and typically is a delayed event that occurs 6 to 18 months after treatment. Risk factors for radionecrosis include the prescription dose, size of the target, age of the patient, and number of brain metastases treated. Imaging features of radionecrosis are often difficult to distinguish from tumor progression and characteristically entail increased patchy enhancement with an increase in surrounding edema (Fig. 3). Advanced imaging techniques such as magnetic resonance perfusion may be helpful for distinguishing the two. The majority of the time, the changes of radionecrosis are asymptomatic, but it may lead to a range of neurologic deficits corresponding to the involved region of the brain.[87-89] Cumulatively, severe radiation necrosis from 1 or more sites can lead to devastating neurocognitive decline. This risk may increase because patients are living longer with more effective systemic agents.

Retrospective data on radiation necrosis in the setting of immunotherapy with SRS versus targeted therapy with SRS are conflicting and inconclusive.[90-94] In the absence of prospective studies, it is impossible to conclude that SRS in combination with systemic therapy increases the risk of radiation necrosis. Acutely, increased expression of inflammatory cytokines TNF-α and VEGF in the setting of radiation can lead to disruption of the blood-brain barrier and result in edema.[95] Radiation-induced vessel injury is a chronic effect of radiation.[96-98] Steroids and VEGF inhibitors such as bevacizumab are typically the treatment for symptomatic radiation necrosis.[61,62,99-104]

Despite retrospective and small prospective studies describing the efficacy of VEGF inhibitors in the setting of radiation necrosis for decreasing edema and associated symptoms, the decision to initiate treatment can be difficult.[62,102,105,106] Levin et al[102] reported that all patients who received bevacizumab for the treatment of radiation necrosis had decreased MRI findings and neurologic symptoms or signs associated with radiation necrosis. At a median of 10 months after the end of treatment with bevacizumab, only 2 patients experienced a recurrence of the MRI findings, and those 2 patients re-initiated bevacizumab. In patients with MBMs, which can be associated with hemorrhagic metastases, the decision to add a VEGF

TABLE 3. Summary of Neurologic Immune-Related Adverse Effects

Adverse Event	Ipilimumab	Nivolumab	Pembrolizumab
Sensory neuropathies	✓		✓
Motor neuropathies	✓		
Guillain-Barre syndrome	✓	✓	✓
Myasthenia gravis	✓	✓	✓
Aseptic meningitis with CSF lymphocytosis	✓		
Inflammatory myopathies	✓		
Dizziness		✓	
Peripheral neuropathies		✓	
Facial/abducens nerve paralysis		✓	

Abbreviation: CSF, cerebrospinal fluid.

inhibitor is difficult, and it should be reserved for patients without a risk of bleeding and with uncontrollable symptoms from the effects of radiation necrosis. However, in patients who cannot receive steroids, bevacizumab can be used in place of steroids with similar effects.

Immune-Related Adverse Effects

Immune checkpoint inhibitors are the backbone of treatment for melanoma in both the metastatic setting and the adjuvant setting. While expanding therapeutic options for melanoma, they have also introduced a spectrum of irAEs targeting any organ in the body. Neurologic irAEs are rare and vary with the mechanism of the immune checkpoint inhibitor (Table 3). They are most likely from T-cell reactivity against antigens expressed by both tumor cells and neurons, although it is also suspected that immune checkpoint inhibitors could unmask an underlying autoimmune condition. Neurologic irAEs affect 2% of patients treated with anti-PD1 therapy alone and 2% to 3% of patients treated with anti-PD1 and anti-CTLA4 combination therapy.[107] The incidence is likely inaccurate because of the lack of recognition in the early trials.[108,109] One of the largest retrospective studies of irAEs examined a total of 3763 patients and 35 patients with 43 types of neurologic irAEs.[110] The results were used to characterize the types of irAEs and the median times to onset and resolution, which were 45 and 32 days, respectively. The analysis emphasized encephalitis as one of the most serious irAEs with 4 reported cases, 1 of which was fatal.

The literature describing neurologic irAEs is growing. Overlap syndromes with multiple concurrent irAEs are common, and the diagnosis of each can be challenging. Early recognition is critical. Treatment involves holding further doses of immune checkpoint inhibitors and starting corticosteroids. Secondary immunosuppression is required for severe cases.

CONCLUSIONS

Neurologic complications from melanoma are not uncommon. These effects may be direct consequences of the disease or the treatment. The specific patterns of presentation include distinct clinical signs and symptoms, radiographic findings, and pathologic diagnoses. Treatment options to address complex patients with neurologic involvement are expanding to include genomically targeted approaches and immune modulation with immune checkpoint inhibitors combined with radiation and other novel agents and ACT. Recognition and a skilled multidisciplinary approach to caring for these patients and assessing the risks and benefits of treatment will lead to the most optimal outcomes.

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