Imaging of Neurologic Injury following Oncologic Therapy

Tao Ouyang, MD[a,b,*], Sangam Kanekar, MD[b,c,d]

KEYWORDS

• Radiation therapy • Radiation necrosis • Chemotherapy • Immunotherapy
• Immune check point inhibitor • CAR-T therapy • SMART syndrome • Methotrexate • Temozolimide

KEY POINTS

- Neurologic injury arise from treatment of central nervous system malignancies (primary and secondary) as result of direct toxic effects or indirect vascular, autoimmune, or infectious effects.
- Neuro-oncologists, radiation oncologists, and radiologists are likely to encounter an increase in number of patients with treatment-induced complications given increased survival rates and increased treatment options, including novel immunotherapies.
- Neurocognitive effects can occur in patients who live more than 6 months after radiation therapy and have been best described in children.
- Central nervous system complications of chemotherapy include aseptic meningitis, stroke-like syndromes, posterior reversible encephalopathy syndrome, dural sinus thrombosis, transverse myelopathy, and delayed leukoencephalopathy.
- Immunotherapy in neurologic tumors currently include check point inhibitors, vaccines, viral therapy and chimeric antigen receptor T-cell therapy.

INTRODUCTION

Primary and secondary central nervous system (CNS) malignancies present a treatment challenge owing to overall poor prognosis and presence of blood brain barrier. Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, with a 2-year survival rate of approximately 17% and current median survival of 15 months. Close to 20,000 patients are diagnosed in the United States with GBM each year. Brain metastasis occurs in 8% to 10% of adult patients with cancer. The common primary malignancies that metastasize to the brain are lung, breast, and melanoma. Additional cancers with brain metastases include renal cell, colorectal cancer, and gynecologic cancers. Brain metastases are typically associated with advanced stage cancer. With improvement in the survival of patients with systemic cancers, it is expected that incidence of brain metastasis will only increase. Mainstream treatments for CNS malignancies include resection, radiation, chemotherapy, immunotherapy, and combination treatments.

In general, treatments have improved outcomes in some malignancies, especially lymphoma, leukemia, and melanoma.[1] Survival for malignant glioma has not significantly improved in the past 3 decades despite advances in treatment. Brain metastases are associated with a poor prognosis similar, to that of GBM, with a median survival of

[a] Department of Radiology, Penn State Health, Hershey, PA, USA; [b] Division of Neuroradiology, Penn State Milton Hershey Medical Center, Penn State College of Medicine, Mail Code H066 500 University Drive, Hershey, PA 17033, USA; [c] Department of Radiology, Penn State College of Medicine, Hershey, PA, USA; [d] Department of Neurology, Penn State College of Medicine, Hershey, PA, USA
* Corresponding author. Division of Neuroradiology, Penn State Milton Hershey Medical Center, Penn State College of Medicine, Mail Code H066 500 University Drive, Hershey, PA 17033.
E-mail address: touyang@pennstatehealth.psu.edu

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about 12 to 15 months. Despite major advances in oncologic diagnosis and treatment, the survival time for patients treated with radiation therapy remains at 3 to 6 months. Overall survival is often determined by the extent and activity of the primary tumor.

Unfortunately, all oncologic therapies are to some extent neurotoxic. Neurologic injury arise from treatment of CNS malignancies (primary and secondary) as result of direct toxic effects or indirect vascular, autoimmune, or infectious effects. Multimodality treatment may potentiate both therapeutic and toxic effects. Symptoms range from mild to severe and permanent and can be greatly debilitating to patients and their caregivers. Injuries can be immediate or delayed. Neuro-oncologists, radiation oncologists, and radiologists are likely to encounter an increase in the number of patients with treatment-induced complications given the increased survival rates and increased treatment options, including novel immunotherapies.

Many of the early complications are nonspecific and either do not require imaging for diagnosis or have no definite radiographic correlate. These complications include headache, nausea, vomiting, dizziness, confusion, dystonia, Parkinsonian symptoms, cerebellar syndrome, tremors, and seizures. Other early and delayed neurologic injuries, such as posterior reversible encephalopathy syndrome (PRES), dural sinus thrombosis, infarctions, myelopathy, leukoencephalopathy, and hypophysitis, have unique imaging features.

This article reviews the current treatment options for CNS malignancies and common and uncommon neurologic injuries that can result from treatment, with a focus on radiologic features.

RADIATION THERAPY

Radiation therapy remains mainstay of treatment for primary and secondary CNS malignancies. Approximately 200,000 patients per year receive radiation yearly in the United States.[2] Currently, photons, electrons, and protons are all used in particle-based radiation therapy. Cranial radiation therapy may be delivered externally or be injected or implanted. Treatment may be targeted or whole brain based, and administered as a single fraction or fractionated. Regardless, all radiation therapy relies on DNA breakage as the mechanism of cell death.

Whole brain radiation therapy is used for brain metastasis. It is administered to the entire brain, usually over multiple treatments. Local field external beam radiation is used for malignant gliomas because the overwhelming majority of recurrences occur at or immediately adjacent to the original tumor. Stereotactic radiosurgery delivers precisely targeted radiation to brain lesions and can be used for both metastases and primary brain tumors. For high-grade gliomas, adjuvant radiation therapy after maximal safe resection improves local control and survival. Involved field radiation therapy delivers radiation to the tumor or tumor bed plus a margin of radiographically normal tissue. The standard dose for GBM is 60 Gy given over 6 weeks in 2-Gy fractions, usually with concurrent chemotherapy. For anaplastic astrocytoma (World Health Organization grade III), usually a slightly lower total dose is used in slightly smaller fractions.

Particle radiation (neutrons, helium ions, and protons) have been studied as boosters to conventional radiation therapy. The theoretic advantage to these particles are finite path lengths and the ability to concentrate the majority of their dose at the end of their path length, with little exit dose. This feature potentially decrease radiation exposure of normal surrounding tissue. Proton radiation is commonly used to treat pediatric CNS tumors, such as medulloblastoma, but its superiority in other CNS malignancies is not established. Similarly, brachytherapy, which is the placement of radioisotope seeds in the tumor or surgical cavity, is of limited usefulness in malignant gliomas.[3,4] Malignant gliomas tend to be infiltrative tumors, and brachytherapy delivers high-dose radiation to areas located few millimeters from the seeds; therefore, it does not adequately reach the full extent of disease.

Sheline[5] was the first to classify the radiation-induced side effects according to their time of appearance after irradiation into acute disorders (days to weeks), early–delayed complications (1–6 months), and late–delayed complications (<6 months). The mechanism of radiation therapy-induced damage to the CNS seems to be complex and likely to include a combination of vascular injury, demyelination, neuronal damage, effects on the fibrinolytic enzyme pathway, and immune mediated.[6] The vascular injury is thought to be partly responsible for the abnormal vasculature, thrombosis, and fibrinoid necrosis eventually leading to radiation necrosis. Radiation therapy also causes cell depletion, especially oligodendrocytes, which in turn leads to demyelination and white matter necrosis. Other cells such as neurons, astrocytes, and microglia are also damaged. Other factors that increase the risk of radiation-induced toxicity are older age, concurrent diseases (such as diabetes and hypertension), vascular disease, concurrent chemotherapy, and genetic predisposition. In

stereotactic radiosurgery, additional risk factors include dose, treatment volume, location of lesion(s), and concurrent systemic treatment.[7]

In the human body, different cell systems have different sensitivity to the radiation. Cells that are actively reproducing are more sensitive to radiation therapy than those that are not. Blood cells that are constantly regenerating are, therefore, most sensitive, whereas nerve and muscle cells are the slowest to regenerate and therefore are least sensitive to radiation. Although the vascular endothelial cells and oligodendrocytes have been regarded as direct primary targets of radiation, the overall effect is thought to be multifactorial and attributed to more than 1 cell lineage.

Early Complications of Radiation Therapy

Many of the early complications are nonspecific and without radiographic features, including fatigue, headache, local skin reaction, alopecia, nausea and vomiting, dizziness and vertigo, and anorexia. Some patients present with acute encephalopathy and seizures without imaging correlates. Focal neurologic deficits and seizure in some cases can worsen owing to cerebral edema can be seen in some cases, especially when the treated lesion is larger in size and after stereotactic radiosurgery, and can account for symptoms within 2 weeks of treatment. Other complications include serous otitis and parotitis.

Delayed Complications of Radiation Therapy

Pseudoprogression refers to treatment effects that mimic the appearance of tumor progression, often occurring in the first 3 months after treatment. Pseudoprogression is more common in patients with *MGMT*-methylated GBM. Differentiating psuedoprogression from true progression is a particular challenge in the interpretation of surveillance MR imaging. Radiation necrosis (RN) is the delayed effect of radiation therapy that can occur anywhere from 1 to 10 years after treatment, with the peak period between 1 and 3 years. On MR imaging, RN can have a confusing and bizarre appearance with hyperintensity on T2-weighted (T2W) imaging and fluid attenuation inversion recovery (FLAIR) imaging, edema, and marked enhancement. Knowledge of the radiation therapy history and plan is helpful to differentiate RN from true progression. Advanced MR techniques are also helpful, especially perfusion and spectroscopy, because the cerebral blood volume will be low in RN and spectroscopy will demonstrate elevated lactate without elevation of choline (**Fig. 1**). Necrosis seems to be dose dependent and tends to occur at or near the site of treatment. RN can occur in more distant sites, such as the inferior frontal lobes and brain stem in patients treated for nasopharyngeal carcinoma. Pseudoprogression and RN are discussed in detail elsewhere in this issue.

Stroke, cavernous malformations, and hemorrhage can occur as a delayed complications of radiation therapy, especially in patients who received radiation therapy at a younger age or received high doses, with irradiation of the circle of Willis region. Stroke has been noted in both pediatric and adult patients and seems to be associated with dose to the circle of Willis.[8] Moya moya–like disease has been reported approximately 3 to 4 years after radiation therapy and is found in higher rates in children and those with neurofibromatosis type 1.[9] Cavernoma develops approximately 3 to 6 years after radiation therapy and may grow over time; occasionally, they can hemorrhage and cause edema. The typical MR imaging appearance of cavernoma is of a relatively well-defined lesion with heterogeneous T1-weighted (T1W) signal owing to subacute blood products and a T2W hypointense rim. There is exuberant blooming on susceptibility weighted imaging sequences (**Fig. 2**). Usually, there is little or no surrounding edema, unless there is a recent hemorrhage.

Stroke-like migraine attacks after radiation therapy syndrome is a delayed complication characterized by complex neurologic signs and symptoms in patients with history of chemoradiotherapy, usually whole brain radiation. It has been reported in patients ranging from 6 to 30 years after radiation treatment. Patients present with subacute onset of stroke-like symptoms, such as homonymous hemianopsia, hemiplegia, aphasia, and/or seizures. MR imaging reveals cortical edema and gadolinium enhancement, often leptomeningeal, not following any particular vascular distribution (**Fig. 3**).[10] Findings are potentially confusing for tumor progression or recurrence. It is still a poorly understood entity. The majority of patients have resolution of symptoms over the course of several weeks, with resolution of radiographic abnormalities, but up to 45% can have residual deficits.[11] Stroke-like migraine attacks after radiation therapy syndrome can also recur.

Pituitary and hypothalamic dysfunction are common after radiation therapy and may occur in up to 80% of patients, with grown hormone deficiency being the most commonly encountered complication in children.[12] Young and pediatric patients with sellar and/or suprasellar disease may experience hypothalamic hyperphagia and obesity after treatment.

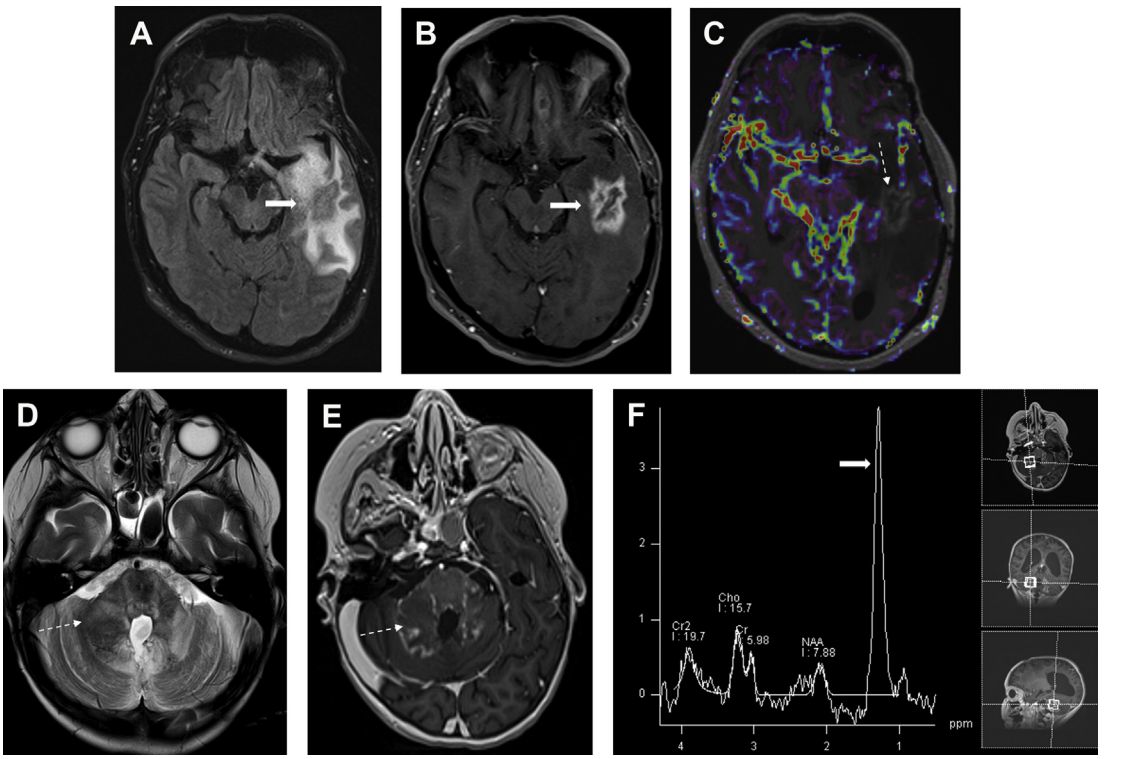

Fig. 1. Two cases of RN. Axial FLAIR (*A*) and T1 post-contrast (*B*) shows edema surrounding an enhancing lesion in the left temporal lobe (*solid arrows*). Enhancement pattern is peripheral and feathery. MR perfusion with overlay (*C*) shows low CBV (*dotted arrow*). Axial T2W (*D*) and T1 post-contrast (*E*) images from another patient shows faint irregular peripheral enhancement in the right cerebellum and brachium pontis (*dotted arrows*), MR spectroscopy (*F*) of the same region reveals a large lactate peak at 1.3 ppm (*solid arrow*) without choline elevation.

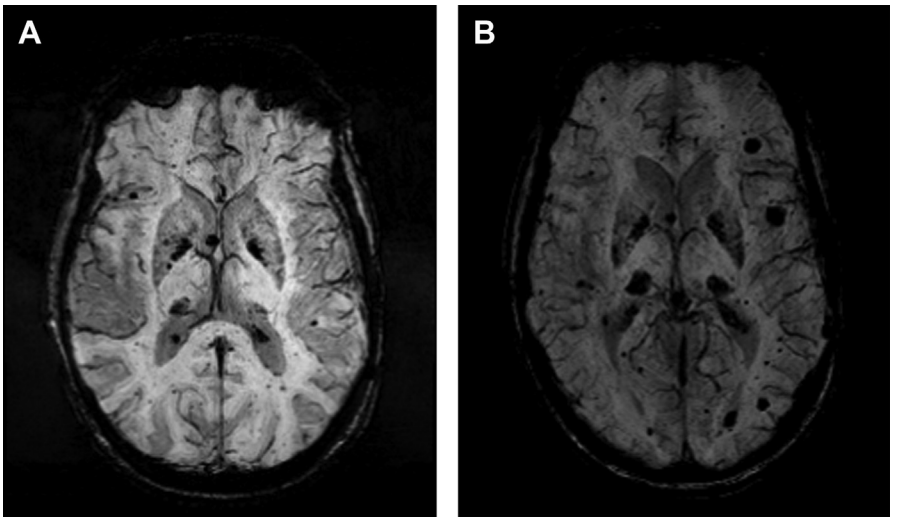

Fig. 2. Radiation-induced cavernomas. A 51-year-old male patient was treated with whole brain radiation therapy for a pineal tumor in 2014. Postradiation axial susceptibility weighted imaging (in 2019) (*B*) shows interval development of multiple cavenomas. Preradiation axial susceptibility weighted image from 2014 (*A*) for comparison.

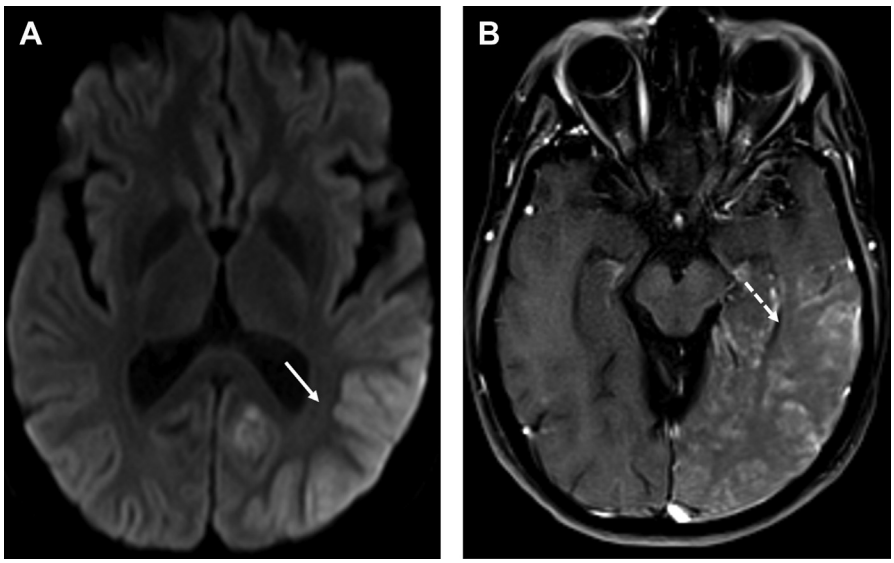

Fig. 3. Stroke-like migraine attacks after radiation therapy (SMART) syndrome. A 28-year-old woman with a history of medulloblastoma presented with headache and stroke-like migraine. Axial FLAIR image (*A*) shows left posterior temporal and occipital cortical hyperintensity and mild swelling (*arrow*) with corresponding cortical enhancement (*dotted arrow*) on the postcontrast T1WI (*B*).

Delayed radiation effects on the spinal cord can present as a myelopathy syndrome or a lower motor neuron syndrome. Imaging shows T2W hyperintensity of the spinal cord with or without enhancement and follow-up imaging shows volume loss indicating myelomalacia.[13] Rarely, patients can present with cord hemorrhage, thought to be from an underlying radiation-induced vascular malformation (**Fig. 4**).

Radiation-induced malignancy is a dreaded late complication of wide field radiation. Malignancies that can develop include meningioma, glioma, sarcoma, and nerve sheath tumor (**Fig. 5**). These may occur anywhere from 5 years to decades after treatment and are a serious concern for patients with long expected survival after primary malignancy. This entity is less of a concern in patients with metastatic CNS disease or GBM, whose

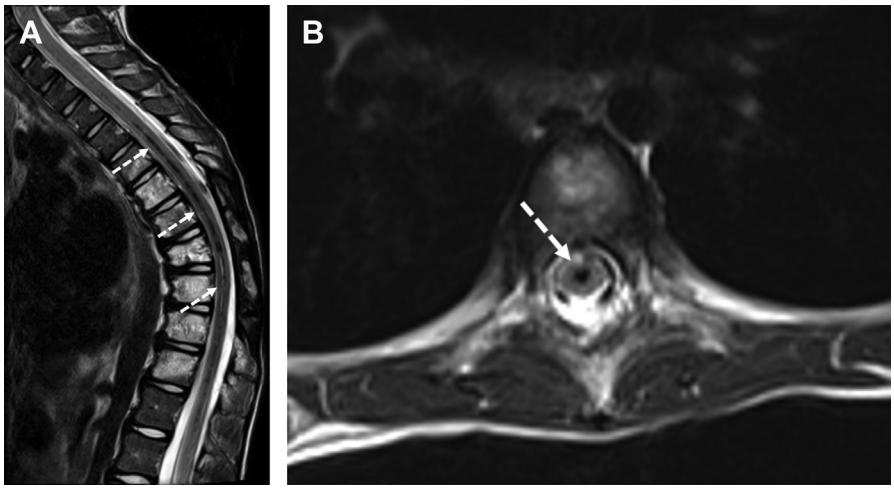

Fig. 4. Radiation-induced hematomyelia. Sagittal and axial T2W images (*A*, *B*) through the thoracic cord shows mild expansion of the cord and low signal owing to hemorrhage within the central portion (*arrows*) along with syrinx.

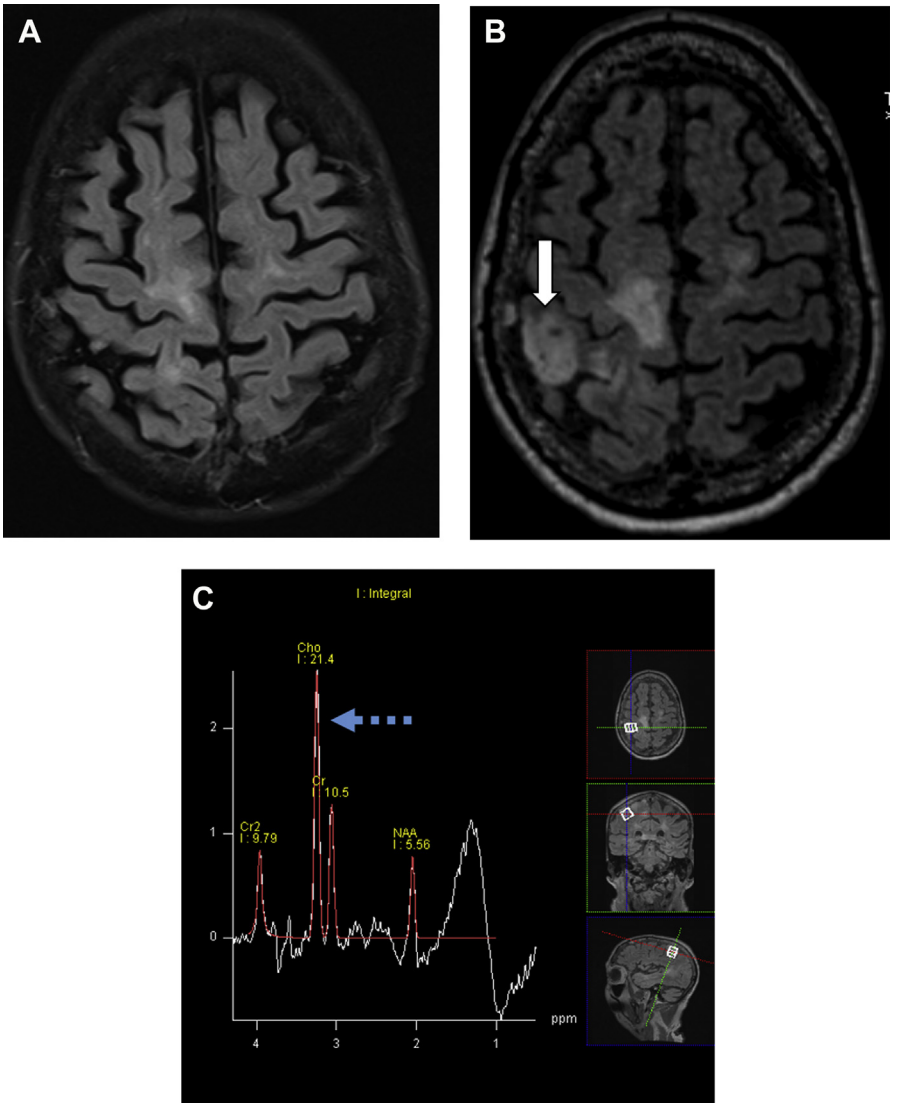

Fig. 5. Presumed post radiation secondary glioma in a patient treated with whole brain radiation for cerebral metastasis. Axial FLAIR (*A*) shows no mass lesion in the bilateral cerebral parenchyma. Four years follow up MRI, axial FLAIR (*B*) shows mass lesion in the right post central gyrus, with elevated choline peak (*dotted arrow*) on MR spectroscopy (*C*).

expected survival is often (much) shorter than 5 years. It is possible that narrow field radiation such as stereotactic radiosurgery may be associated with a lower incidence of secondary malignancy. Outcomes comparing photon versus proton based therapies are lacking.

Neurocognitive effects can occur in patients who live more than 6 months after radiation therapy and have been best described in children who survived brain tumors or acute lymphocytic leukemia.[14,15] Children, especially those who were treated with high-dose chemoradiotherapy before age 6, showed lower scholastic achievement and lower IQ. This effect seems to be dose dependent based on research with children with high- versus low-risk medulloblastoma.[16] In adults, whole brain radiation therapy has also been linked to decline in memory and learning functions in patients with non-small cell lung cancer.[17] Radiographic findings include nonspecific white matter FLAIR hyperintensity and brain atrophy (**Fig. 6**). The relationship between partial brain radiation and neurocognitive decline is less well-established, and targeted radiotherapies may decrease the effect on cognition.

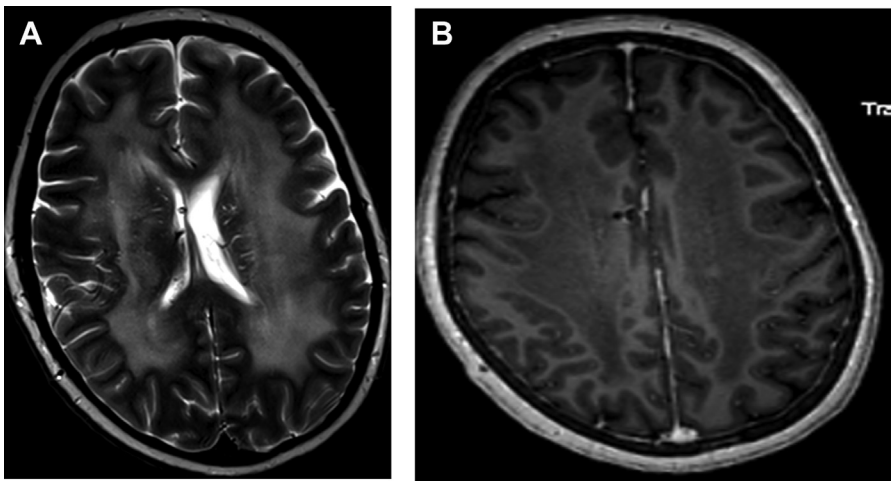

Fig. 6. Radiation leukoencephalopathy. Axial T2W (*A*) and axial T1W (*B*) images show diffuse hyperintensity and hypointensity respectively of the cerebral white matter owing to radiation-induced demyelination.

CHEMOTHERAPY

Chemotherapy, both systemic and intrathecal, and often in combination, remains some of the most effective and widely used treatments for cancer. There are many classes of chemotherapy agents based on their mechanism of action, and many are known to cause neurologic complications. Complications can be acute (during treatment or within 50 days from end of therapy), subacute or delayed (within 3 months of therapy), and late (beyond 3 months). Peripheral neuropathy is most common chemotherapy associated neurotoxicity, especially with platinum based agents. Taxanes and vinca alkaloid agents are also associated with sensory neuropathy, and vincristine has been associated with autonomic and cranial neuropathies.[18]

CNS complications include aseptic meningitis, stroke-like syndromes, PRES, dural sinus thrombosis, transverse myelopathy, and delayed leukoencephalopathy (**Fig. 7**). Methotrexate (MTX) CNS toxicity is best described, but other antimetabolites can cause optic neuropathy, cerebellar syndrome, acute encephalopathy, and cerebral venous thrombosis and venous infarction or hemorrhage in the brain.

Methotrexate

MTX is a frequently used chemotherapy agent and is one of the few approved for intrathecal injection. It works by reducing the amount of tetrahydrofolate available for DNA synthesis, ultimately leading to cell death. There are several well-described MTX-related neurologic complications, including aseptic meningitis, transverse myelopathy, and toxic and necrotic encephalopathy syndromes. Aseptic meningitis is the most common acute CNS toxicity from MTX after intrathecal administration. Symptoms develop as soon as 2 to 4 hours after receiving MTX and usually resolve after 72 hours. Cerebrospinal fluid analysis and MR imaging are usually unrevealing and not required for diagnosis.

Acute toxic encephalopathy after MTX administration has characteristic radiologic findings of restricted diffusion in the white matter, usually affecting the periventricular white matter or centrum semiovale. Usually there is little edema or enhancement. These areas maybe hyperintense on T2W and FLAIR imaging, but sometimes may have little signal change on these sequences. Abnormalities on diffusion-weighted imaging are the hallmark for this diagnosis (**Fig. 8**). Imaging findings may be seen shortly after administration of systemic or intrathecal MTX and is usually reversible.

An acute transverse myelopathy has also been described with MTX, with resemblance radiologically to subacute combined degeneration. Hyperintense T2W and short T1 inversion recovery signal is seen in the spinal cord, predominantly affecting the dorsal columns. There can be variable enhancement, if any (**Fig. 9**). Acute myelopathy is variably reversible. It does not seem dose dependent, suggesting that patient factors maybe at play, and seem to be associated with advanced or young age and prior spinal radiation.[19,20]

A much more debilitating delayed complication of systemic and intrathecal MTX therapy is delayed multifocal necrotizing leukoencephalopathy, which can occur months to years after

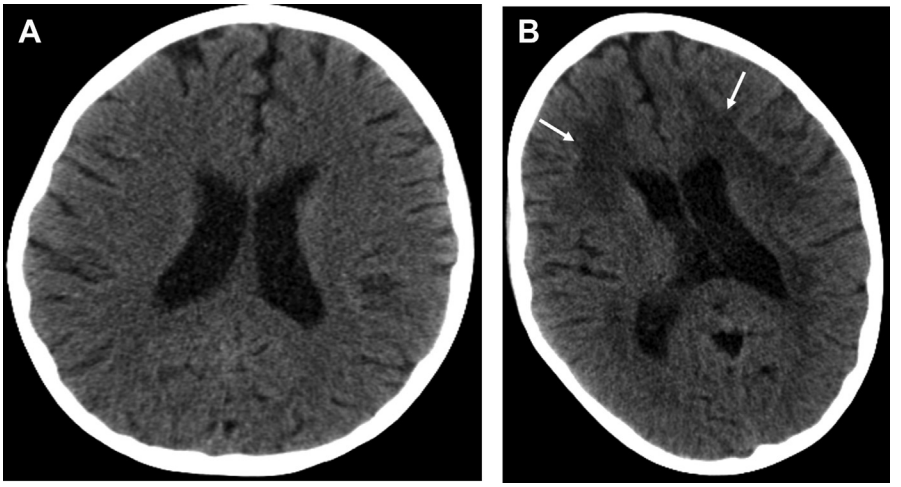

Fig. 7. Postchemotherapy leukoencephalopathy. Prechemotherapy CT scan of the 35-year-old male patient with acute lymphocytic leukemia (ALL) treated with chemotherapy. A follow-up scan at 2 years shows diffuse hypodensity of the cerebral white matter owing to chemotherapy-induced demyelination.

treatment.[19] The patient presents with severe dementia with personality changes. MR imaging shows brain atrophy, confluent white matter, FLAIR hyperintensity, necrosis, and patchy areas of enhancement. Usually, this complication occurs after repeated high-dose MTX or combined MTX and radiation therapy.

Temozolimide

Temozolimide, an alkylating agent, deserves special discussion because it is now part of the standard therapy for malignant gliomas and is also sometimes used in low-grade gliomas. Its mechanism of action seems to be methylation of DNA, leading ultimately to the apoptosis of tumor cells. The standard treatment for malignant glioma is concurrent radiation with temozolomide, followed by at least 6 months of adjuvant temozolimide.[21] Longer term low-dose temozolimide as maintenance therapy is often used. Acute toxicity includes nausea, thrombocytopenia, and leukopenia.[22] The primary radiographic complication of temozolimide is potentiation of pseudoprogression in the setting of concurrent chemoradiation. Some studies have shown that MGMT promoter methylation in gliomas is a predictor of response to temozolimide.[23]

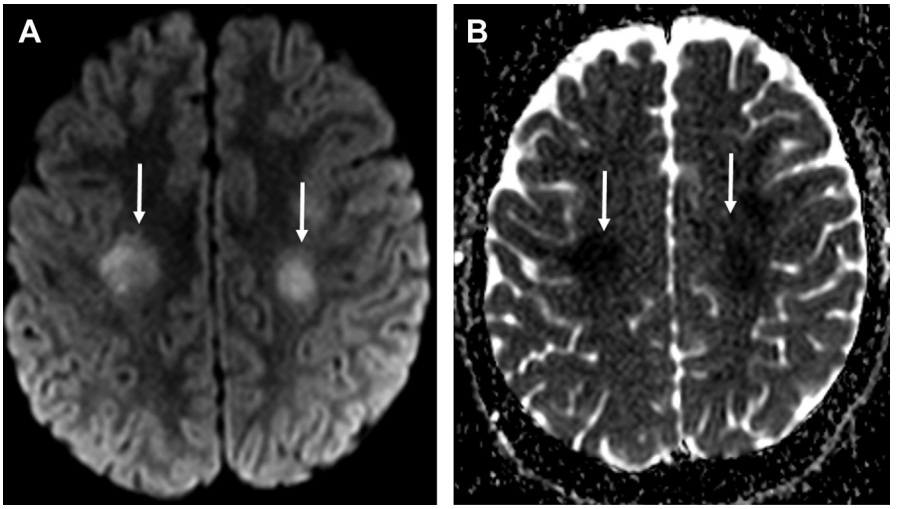

Fig. 8. Acute methotrexate demyelination. Axial DWI and ADC images (*A, B*) show focal areas of restricted diffusion in the centrum semiovale bilaterally (*arrows*) in a patient treated with intrathecal methotrexate for ALL four days prior to MRI. Patient presented with sudden onset of transient paresis.

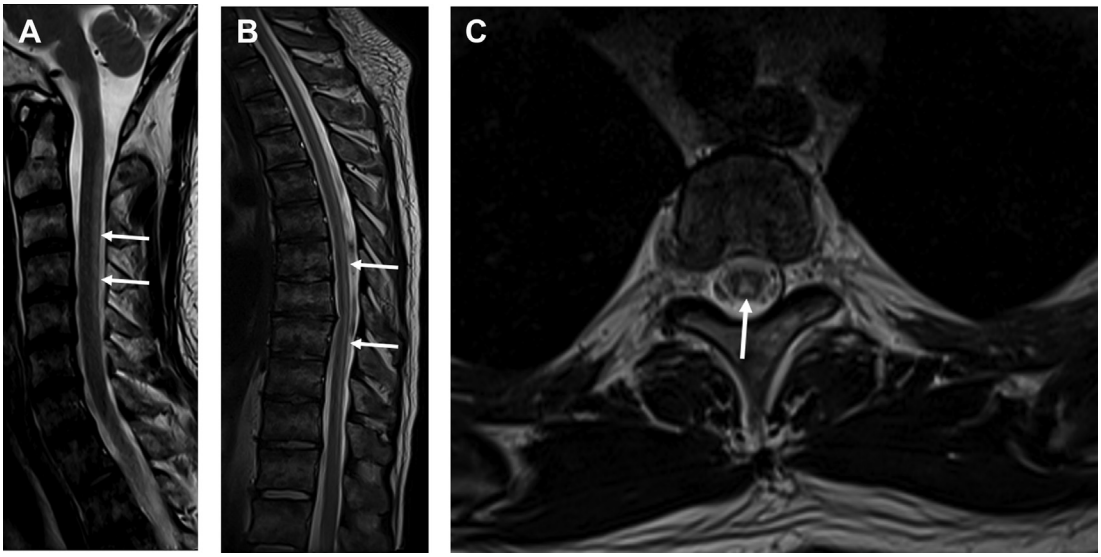

Fig. 9. Acute MTX-induced myelitis. Acute onset paraparesis in a patient within 48 hours of intrathecal instillation of methotrexate. Sagittal and axial T2 image of the cervical (*A*), and thoracic spine (*B, C*) shows linear T2 hyperintensity in the dorsal columns of the cervical cord and the central thoracic cord (*arrows*).

There is also interest in the combination chemotherapies with temozolimide for GBM and anaplastic astrocytoma, as well as for recurrent GBM with MGMT promoter methylation.[24] Additional agents being investigated include vincristine, CCNU, and procabazine. CCNU is also being studied as combination therapy with bevazimumab in recurrent GBM.[25]

Targeted Agents

Targeted agents are the newest frontier in chemotherapeutics and more than 100 new agents have been approved in the last decade.[26] These include 20 classes of tyrosine kinase inhibitors (eg, imatinib, sunitinib, and sorafenib) and monoclonal antibodies (bevacizumab, rituzimab, and alemtuzumab). These newer agents also cause neurologic side effects, some similar to conventional chemotherapy agents, including headache, fatigue, cranial and peripheral neuropathies. In addition, tyrosine kinase inhibitors are associated with a small risk of spontaneous subdural hematomas. Both rituzimab and alemtuzumab, which are antibodies against CD20 and CD25, respectively, have been associated with progressive multifocal leukoencephalopathy with JC virus reactivation.[27,28] The vascular endothelial growth factor targeting agents can cause hypertension and PRES as well as an increase the risk of ischemic stroke.[27]

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor-A, a highly expressed proangiogenic factor in gliomas. Targeting vascular endothelial growth factor decreases tumor vascularity. Bevacizumab is now often used in patients with malignant glioma with radiographic disease progression after completing standard concurrent chemoradiation. Decreased contrast enhancement, edema, and permeability can be seen as early as 1 day after initiation of bevacizumab therapy. Radiologic response rates are high, ranging from 25% to 60%. Despite remarkable imaging response after bevacizumab, there has been no proven substantial benefit in overall survival.[29] Bevacizumab is associated with PRES as well as a phenomenon called pseudoresponse, where tumoral enhancement improves significantly but progression ultimately manifests as nonenhancing, FLAIR hyperintense disease. Development of nonenhancing restricted diffusion within the tumor and vicinity has been termed coagulative necrosis and has been associated with a poorer prognosis.[30]

PRES is thought to be related to failure of autoregulation of cerebral blood pressure and local CNS inflammation. PRES was originally described in uncontrolled hypertension, eclampsia, and patients undergoing immunosuppression for organ transplantation.[31] Patients present with headache, confusion, visual changes, or seizures. MR imaging typically demonstrates focal regions of symmetric hemispheric white matter edema. The parietal and occipital lobes are most commonly affected, followed by the frontal lobes, the inferior

temporal–occipital junction, and the cerebellum. These areas are usually hypointense on T1W imaging and hyperintense on T2W and FLAIR imaging. The subcortical U fibers are often affected. There may be associated restricted diffusion and/or hemorrhage (**Fig. 10**). PRES is seen more commonly in patients receiving cyclosporine and cyclophosphamide and targeted gents such as bevacizumab, ipilimumab, sunitinib, and rituximab. Treatment is symptom based, as well as removal of the suspected causative agent. The clinical and radiographic changes of this syndrome are usually reversible unless cerebral infarction has occurred.

Cerebral venous sinus thrombosis is a potentially devastating entity that can lead to venous infarction and hemorrhage. It has been associated with chemotherapy regimens including platinum based agents and L-asparaginase. On computed tomography scans, the dural sinus or cerebral vein will appear abnormally hyperdense. On MR imaging, a thrombus in the affected vessel will appear hyperintense on T1W imaging and of varying signal intensity on T2W imaging. A thrombosed vein will appear abnormally hyperintense on FLAIR imaging and drop out on susceptibility weighted imaging, which is classic. Postcontrast T1W images may show a nonenhancing clot within the affected vessel. The brain parenchyma may appear normal or be edematous/ischemic, and in some cases parenchymal hemorrhage will be present (**Fig. 11**).

Progressive multifocal leukoencephalopathy is an infectious process that affects the white matter, caused by reactivation of the JC virus. This virus is present usually in asymptomatic individuals, but in the context of immunosuppression, circulates in B cells and infects and destroys oligodendrocytes. On MR imaging, there are confluent asymmetrical white matter lesions which are hyperintense on T2W and FLAIR imaging, and may not enhance (**Fig. 12**). There is often subcortical U fiber involvement. Appearance is different from PRES in its asymmetry and distribution, with no predilection for the parietal or occipital lobes. Lesions can progress fairly rapidly. Diagnosis is made by cerebrospinal fluid testing and there is no effective treatment.

Many patients who received chemotherapy describe more global neurocognitive impairment that is less dramatic than the multifocal leukoencephalopathy of MTX. This complication is often colloquially termed “chemo brain” and mostly affects short-term memory and executive function. There may be little or subtle radiologic findings, such as diffuse white matter T2W and FLAIR hyperintensity and volume loss. However, there is some overlap between treatment effects and the effect of cancer itself on the brain.

COMBINATION THERAPIES

The use of chemotherapy potentiated effectiveness of radiation by introducing unique and increased DNA aberrations that differ from those induced by either radiation or chemotherapy alone. Unlike conventional chemotherapy, which exerts its cytotoxic effects on all replicating cells, conformal radiation is particularly effective at producing DNA damage specifically in tumor cells.[32] Commonly used chemoradiation regimens include antimetabolites, platinum-based agents, alkylating agents, and, more recently, novel agents such as antibodies and immunotherapy. Antimetabolites

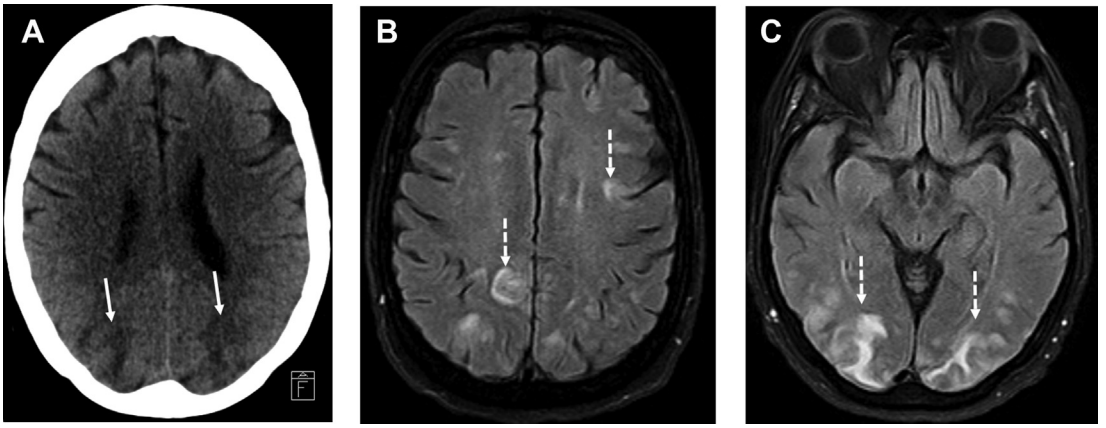

Fig. 10. PRES in patient who was undergoing chemotherapy treatment for leukemia. Axial CT scan (*A*) shows symmetrical hypodensities (*solid arrows*) in the posterior parietal lobe cortex bilaterally. Axial FLAIR (*B, C*) images show bilateral symmetrical hyperintensity in the cortex and subjacent white matter of occipital and frontal lobes (*dotted arrows*).

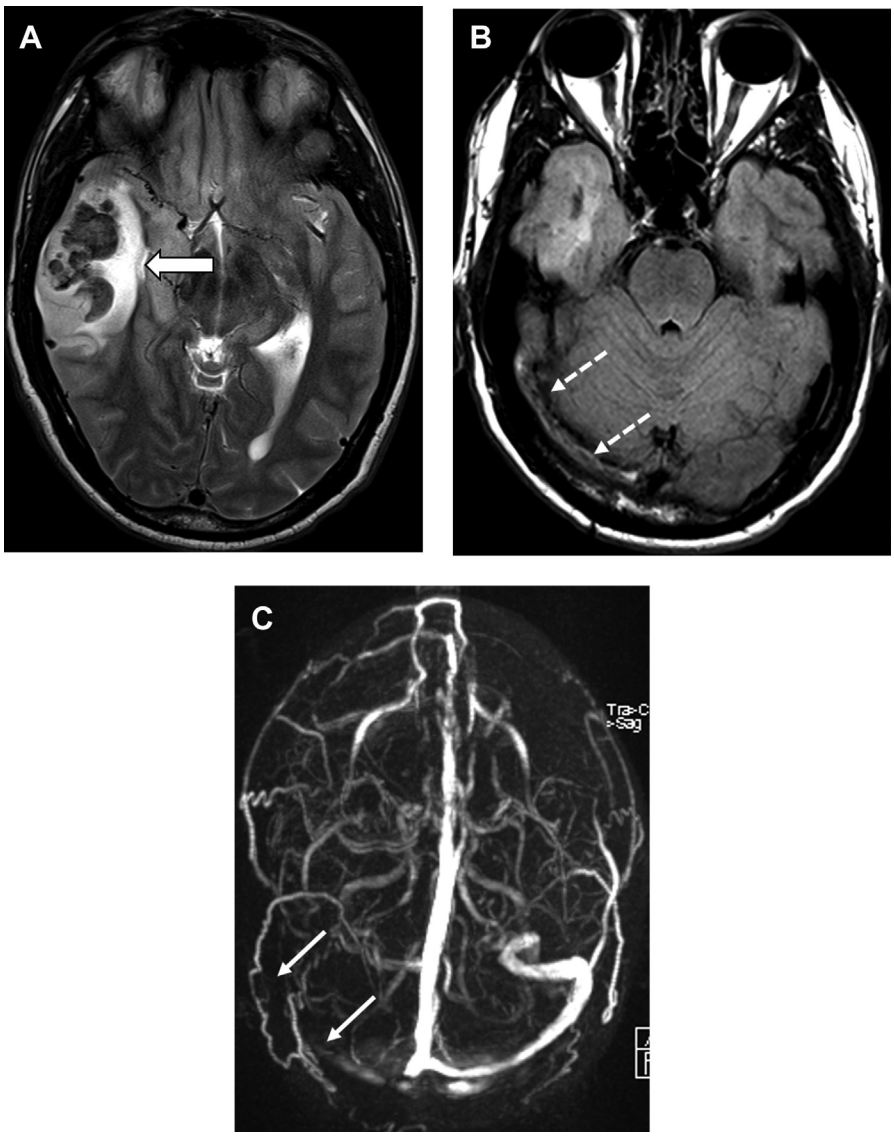

Fig. 11. Cerebral venous thrombosis in patient treated with cisplastin for neuroblastoma. Axial T2W (*A*) shows hemorrhagic stroke in the right temporal lobe (*thick arrow*). Axial FLAIR image (*B*) and MR venogram (*C*) shows thrombosis of the right lateral and sigmoid sinuses, appearing as abnormal FLAIR hyperintense signal (*dotted arrows*) and absence of flow related signal (*solid arrows*) respectively.

are commonly used in combination with radiation. The combination of these agents with radiation leads to the production of complex, slowly repaired radiation-induced DNA damage. Platinum-based agents such as cisplatin are the most widely used chemotherapeutic agents in combination with radiation, especially in lung and head and neck cancers. The standard therapy for GBMs is concurrent temozolomide radiation. Radiosensitization by temozolomide involves inhibition of DNA repair and/or an increase in radiation-induced double-stranded breaks. Other novel agents sensitize tumor cells to radiation by inhibition of the ubiquitin proteosome system (bortezomib) or modulation of tumor oxygen levels and aberrant tumor vasculature (bevacizumab).

IMMUNOTHERAPY

Immunotherapy has become a successful treatment option for many advance cancers, and can be used as stand alone or in combination with other modalities.[33] There are currently more than 500 open immunotherapy clinical trials at the time of this review. The brain is not as immune-privileged organ as previously thought, and

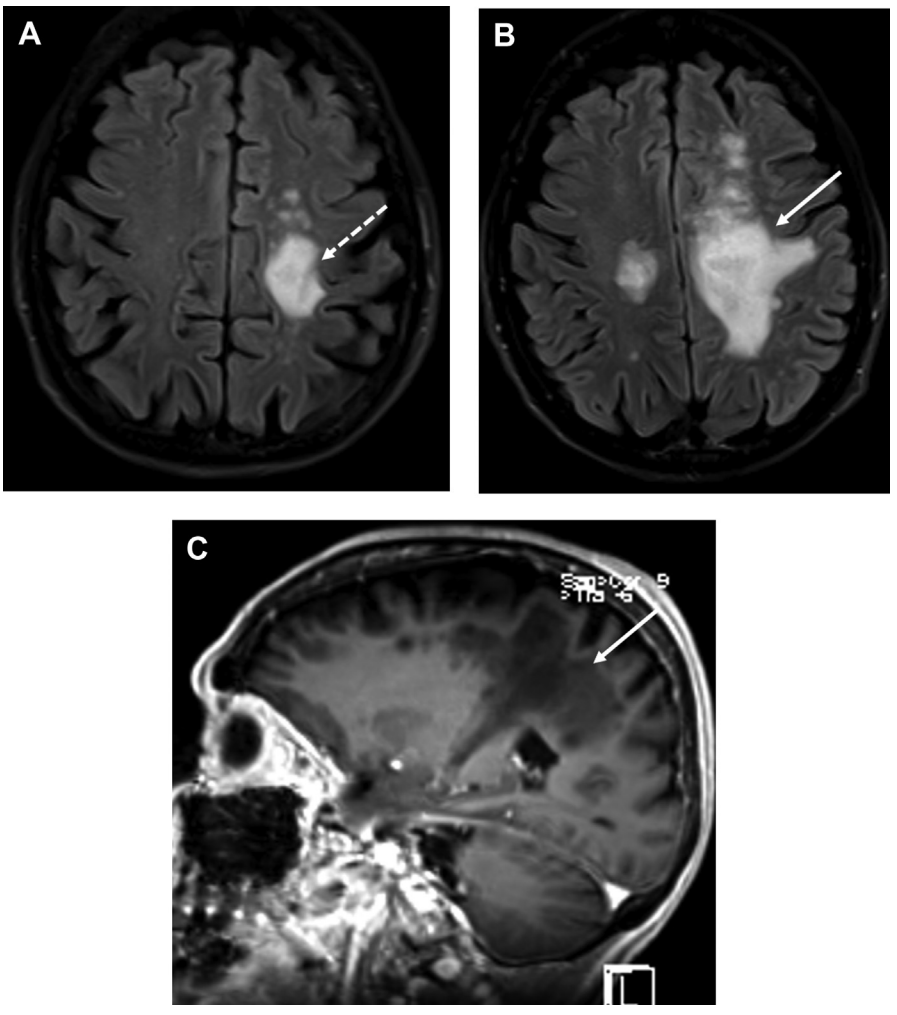

Fig. 12. Progressive multifocal leukoencephalopathy (PML) in 69-year-old male patient on chemotherapy for multiple myeloma. Axial FLAIR image in Aug 2017 (*A*) show a hyperintense PML lesion in the juxtacortical and centrum semiovale of the left frontal lobe (*dotted arrow*). Axial FLAIR and sagittal T1W images in Oct 2017 (*B, C*) show significant increase in the size of the lesions (*solid arrows*) with deterioration of the patient's symptoms.

immune checkpoint inhibitors have been successful for brain metastasis from melanoma and non-small cell lung cancer. Immunotherapy in CNS tumors currently include check point inhibitors, vaccines, viral therapy and chimeric antigen receptor T-cell (CAR-T) therapy.

Immune Check Point Inhibitors

Immune check point inhibition first emerged as a viable option in 2010, with CTLA-4 inhibitor (ipilimumab) in advanced melanoma resulting in improved overall survival.[34] Immune check points are signals (stimulatory or inhibitory) between tumor cells, T cells, dendritic cells, and macrophages in the tumor microenvironment. These checkpoints regulate T-cell activation to tumor cells. It is known that tumors cause immune suppression and "escape" from T-cell–mediated immune responses so they can proliferate within the host.[35] Immune checkpoint inhibitors, including CTLA-4 inhibitor (ipilimumab), programmed death (PD)-1 inhibitors (nivolumab and pembrolizumab), and PD ligand 1 (L1) inhibitors (atezolizumab and durvalumab), counteract against tumor cells and activate the host's immune response against cancer. Currently, these agents are approved for use in the United States for numerous malignancies including melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial cell carcinoma, cervical cancer, colorectal cancers, and breast cancer.

Unique complications associated with use of immunotherapies have been collectively termed immune-related adverse events and can arise in almost any organ system. The mechanism is thought to be immune system activation with misdirection or overactivation. Organ-specific adverse events include hypophysitis, encephalitis, pneumonitis, hepatitis, myocarditis, colitis, and sarcoid-like lymphadenopathy. Neurologic adverse events are uncommon, occurring in 1% to 3% of patients and are mostly nonspecific such as headache, dizziness, and lethargy.[36] Other complications are similar to those from conventional chemotherapy agents and can include aseptic meningitis, acute and subacute encephalopathy, transverse myelopathy, PRES, demyelination, and polyneuropathies.[37] A well-described complication specific to immune checkpoint inhibitors is hypophysitis, with up to 17% of patients receiving ipilimumab developing hypophysitis.[38] On MR imaging, this appears as enlarged and enhancing pituitary gland and stalk that is either new from prior imaging studies and/or abnormal for age (**Fig. 13**).

Chimeric Antigen Receptor T-cell Therapy

CAR-T therapy is currently approved in leukemia and B-cell lymphoma. Essentially, CAR-T cells are genetically modified T cells that recognize a tumor-specific antigen and contains a T-cell activation signal inside the cell. When these modified T cells are introduced to the patient, they initiate lysis of the tumor cells bearing the tumor-specific antigen. The most common toxicity from CAR-T therapy is cytokine release syndrome, which is a systemic inflammatory response. Incidence of neurotoxicity varies greatly in reports, ranging from 0% to 50%,[39] and may occur with and without systemic cytokine release. Neurotoxicity ranges from headaches and delirium to encephalopathy and seizures. Severe cases may require intensive care and dexamethasone treatment. Neuroimaging and cerebrospinal fluid analysis is recommended to exclude an underlying infection.

Immunotherapies in Glioblastoma

The low mutation burden in GBM, local and systemic immunosuppression of GBM, and its infiltrative nature likely account for difficulties in effective treatment of GBM with immune checkpoint inhibitors. GBM is a highly immunosuppressive solid tumor, even though it is confined to the brain. GBM is also highly infiltrative in a way that brain metastases are not. Immune checkpoint inhibitors tend to accumulate in the necrotic center of the tumor there where is more blood–brain barrier breakdown rather the infiltrative margins. The disease is also highly likely to recur. At this time, there are no immunotherapies approved by the US Food and Drug Administration for the treatment GBM, and GBM is notoriously immunosuppressive and immunologically quiet.[40] Checkpoint inhibitors are being studied in combination with other therapies. At the time of this writing, there were 8 published studies of immune checkpoint inhibitor alone and in conjunction with other agents for GBM and 3 yet unpublished studies, none of which found significant benefit in the immune checkpoint inhibitor group.[41] PD-1 and PD-L1 axis inhibitors, such as nivolumab and pembraolizumab, are the best studied immune checkpoint inhibitors in GBM. CTLA-4 and PD-1/PD-L1 dual blockade is also being studied. Another immunotherapy currently being studied is the proteasome inhibitor

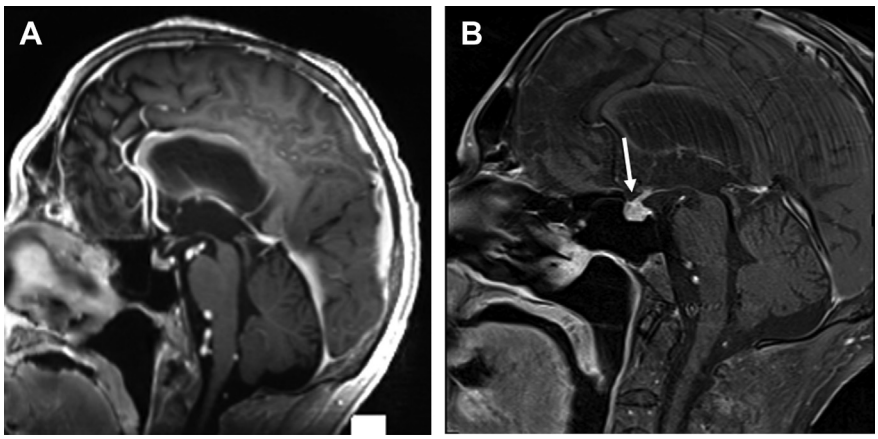

Fig. 13. Ipilimumab hypophysitis in patient with melanoma. Contrast enhanced sagittal T1W image before immunotherapy (*A*) shows normal appearance of the pituitary and infundibulum. There is mild hyperplasia of the pituitary gland (*arrow*) and thickening of the infundibulum after immunotherapy (*B*).

marizomib, which has demonstrated activity against CNS multiple myeloma. Several clinical trial with marizomib for GBM and recurrent GBM are underway.[42]

Other immunotherapies for GBM include vaccine therapy, which is designed to elicit an immune response to the cancer. Vaccines include direct antigen exposure as well as antigen-presenting cells (dendritic cells). The best studied tumor specific antigen is a mutation of epidermal growth factor, epidermal growth factor variant III. The epidermal growth factor mutation is seen in 2% to 25% of GBM. An epidermal growth factor variant III–specific peptide was developed by Celldex therapeutics, rindopepimut. A phase III trial of rindopepimut showed no significant improvement in survival in wither the treatment or the control arms, however.[43] A number of tumor-associated antigens are being studied, including single antigen vaccine called SurVaxM and vaccines targeting multiple antigens such as SI701 and ICT-101. These are currently in phase II and I trials, respectively.[44]

Customized vaccines are also promising. These vaccines are limited to patients with surgically accessible GBM, because a volume of the tumor is required to produce the vaccine, which is then reintroduced to the patient. Two such agents under study are DC-Vax-L and HSPPC-96. Dc-Vax-L, which uses tumor lysate to generate dendritic cells, was first studied 10 years ago with reports of durable responders surviving more than 7 years.[45] Phase III of this vaccine for newly diagnosed GBM is still underway. HSPPPC-96 is in phase II trials.[46] Viral therapy is a form of immunotherapy that virus vectors introduce genes into tumor cells to attract host immune response, ideally leading to tumor lysis. Two of these, ASPECT and Toca5, have made it to phase III trials.[47,48]

CAR-T therapy has been most effective against hematologic malignancies owing to their highly clonal nature and location (peripheral blood). The main challenges in the development of cell therapy in GBM are the location of the tumor, determining the most efficacious route of cell delivery (intravenous vs intrathecal), and the identification of a universal cell surface antigen to target. Tumor antigens that are potential CAR targets in GBM include IL-13Ra2, epidermal growth factor version III, Her2, and EphA2. Several factors contribute to lack of response to CAR T-cells in GBM, including a lack of stably expressed antigens, intratumoral heterogeneity, impaired CAR T-cell proliferation in a hypoxic environment, and an immunosuppressive microenvironment that leads to antigen escape.[49]

PEDIATRIC BRAIN

More than 10,000 children under the age of 14 are diagnosed with malignancy each year. More than 80% of these children are expected to be long-term survivors thanks to advances in modern cancer treatment. Although early neurologic toxicities and complications in children receiving treatment for cancer are similar to adults, higher survival rates and longer post-treatment lifespans mean that neurologic injury is even more impactful in survivors of childhood cancer. Moreover, the developing CNS system of a child is potentially more susceptible to the effects of radiation and chemotherapy, for reasons that have been details elsewhere in this article.

Cranial radiation therapy in pediatric patients with cancer has been associated with serious adverse effects that can lead to poor educational attainment and unemployment in long-term survivors. This has been well-studied in childhood survivors of acute lymphocytic leukemia. Contemporary protocols have now replaced chemoradiotherapy with systemic and intrathecal chemotherapy for acute lymphocytic leukemia, which has decreased the degree of survivors' cognitive impairment. Nevertheless, survivors of childhood acute lymphocytic leukemia displayed more neurocognitive and parent-rated neurobehavioral problems than population norms.[50] Survivors who developed acute leukoencephalopathy during therapy demonstrated more neurobehavioral problems than those who did not.[51]

Survivors of childhood cancer also have significantly higher incidence of secondary CNS neoplasms, primarily glioma and meningioma, compared with the general population. The imaging appearance of these malignancies as same as those occurring in patients without prior cancer treatment. Nearly all cancer survivors who developed a CNS neoplasm had been exposed to cranial radiation, and some studies showed a correlation between radiation dose and risk of subsequent CNS tumors.[52]

SUMMARY

The arsenal of treatments for CNS primary and secondary malignancies continue to grow, even though the mainstay of treatment remains radiation and chemotherapy, especially for malignant gliomas. Targeted and immune therapies are clearly the future of cancer care. All oncologic treatments carry inherent toxicities to the CNS, and many are associated with specific imaging appearances. The job of the neuroradiologist is made more complicated by treatment effects that mimic

tumor progression or response. Moreover, additional neurologic toxicities of newer immunotherapies may yet be discovered as their use becomes widespread. Recognizing these complications and differentiating treatment effects from effects of the cancer itself are priorities for the treating team and can significantly impact the course of treatment and outcome.

DISCLOSURE

None.

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