Iatrogenic Neuropathology of Systemic Therapies

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KEYWORDS

- Iatrogenic • Neuropathology • Neurotoxicity • CAR T cell
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Chemotherapy-related cognitive impairment

Key points

- Chimeric antigen receptor (CAR) T-cell–associated neurotoxicity (immune effector cell–associated neurotoxicity syndrome, ICANS) is closely associated with cytokine release syndrome and might be mediated by elevated circulating cytokines, endothelial activation, and impaired function of the blood-brain barrier (BBB).
- Histologic features of severe ICANS are varied and nonspecific but include perivascular fluid extravasation, platelet microthrombi, hemorrhage, microinfarcts, clasmatodendrosis, gliosis, microglial activation, and inflammatory cell infiltrate of variable extent, distribution, and composition (including CAR T cells).
- Adverse effects of chemotherapy involving the central nervous system (CNS) include leukoencephalopathy and chemotherapy-related cognitive impairment (CRCI).
- The pathogenesis of chemotherapy-induced leukoencephalopathy may involve the direct cytotoxic effect of chemotherapeutic agents on CNS progenitor cells and oligodendrocytes, impaired self-renewal potential of oligodendrocyte precursors exposed to sublethal chemotherapy concentrations, and oxidative stress.
- The pathogenesis underlying CRCI is multifactorial and likely includes elevated proinflammatory cytokines, reactive oxygen species (ROS)/oxidative stress, DNA damage, BBB dysfunction, direct effects of chemotherapy on CNS cells, neuroinflammation, and dysmyelination.

ABSTRACT

Administration of systemic antineoplastic agents can result in adverse neurologic events. We describe the clinicopathologic features and putative mechanisms underlying iatrogenic neuropathology of the central nervous system secondary to chimeric antigen receptor (CAR) T-cell therapy and conventional chemotherapy.

OVERVIEW

Medical therapies and interventions to improve patient morbidity and mortality can result in inadvertent neurologic sequelae. Recently, there has been much attention given to adverse effects secondary to antineoplastic therapies, as demonstrated by newly released National Institute of Health Cancer Moonshot Initiatives, one of which is to "minimize debilitating side effects of cancer and its treatment."[1] This review focuses on the histologic features and underlying mechanisms of the neuropathology associated with 2 types of

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Surgical Pathology 13 (2020) 331–342
https://doi.org/10.1016/j.path.2020.01.004

antineoplastic therapies—chimeric antigen receptor (CAR) T-cell therapy and conventional chemotherapy.

CAR T-CELL THERAPY

Highlights

Clinical:

- Anti-CD19 chimeric antigen receptor (CAR) T-cell therapies show impressive, sustained therapeutic responses to several hematologic malignancies and are Food and Drug Administration approved for relapsed/refractory B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma.
- Adverse effects include cytokine release syndrome (CRS) and neurotoxicity (immune effector cell–associated neurotoxicity syndrome [ICANS]).

Putative Mechanism of ICANS:

- Expansion of CAR T cells after infusion results in release of cytokines, particularly from monocytes/macrophages. Elevated circulating cytokines likely cause endothelial activation and breakdown of the blood-brain barrier (BBB). Additional cytokines may be released from intracranial cell populations (eg, microglia, astrocytes, pericytes, and endothelial cells), potentially exacerbating BBB dysfunction.

Histology:

- Expansion of the perivascular spaces from extravasated fluid, vacuolated/degenerated white matter, gliosis, clasmatodendrosis, platelet microthrombi, fibrinoid vascular necrosis, hemorrhage, microinfarcts, and prominent/activated microglia have been observed in the more acute to subacute setting of ICANS.
- Chronic changes may include gliosis, activated microglia, corpora amylacea, expansion of the perivascular space, evidence of remote hemorrhage, and cortical atrophy.
- Inflammatory cell infiltrates (including CAR T cells, non-CAR T cells, and macrophages) are variable in extent and distribution (eg, perivascular, subarachnoid, meningeal, or intraparenchymal).
- CRS in the absence of ICANS does not seem to have any overt, specific microscopic neuropathology.

Histologic Differential:

- Posterior reversible encephalopathy syndrome, viral encephalitis, cerebral malaria, acute necrotizing encephalopathy, acute hemorrhagic encephalopathy, and environmental toxins, among others.

Chimeric antigen receptor (CAR) T cells are a form of cancer immunotherapy in which autologous or allogenic T lymphocytes are engineered to express recombinant receptors composed of a tumor recognition region, a T-cell receptor intracellular signaling domain, and typically at least one intervening costimulatory domain. Recognition of the target antigen results in activation and proliferation of CAR T cells, leading to release of cytokines and tumor cell apoptosis. Although CAR T cells have been constructed to recognize several different tumor antigens, including mesothelin, Her2, B-cell maturation antigen, and glypican 3, the most promising target has been CD19. Numerous studies have demonstrated that anti-CD19 CAR T cells can produce significant and sustained therapeutic responses in patients with relapsed/refractory B-cell acute lymphoblastic leukemia, B-cell non-Hodgkin lymphoma, and chronic lymphocytic leukemia.[2–8] Reflecting the clinical efficacy of CAR T-cell therapy, the Food and Drug Administration has approved 2 anti-CD19 CAR T-cell products: tisagenlecleucel for use in refractory/relapsed B-ALL or diffuse large B-cell lymphoma (DLBCL) and axicabtagene ciloleucel for use in refractory/relapsed DLBCL.[9]

Despite their therapeutic utility, CAR T cells are associated with several complications such as cytokine release syndrome (CRS) and neurotoxicity (immune effector cell–associated neurotoxicity syndrome [ICANS]). CRS, which can be seen in 35% to 93% of patients receiving CAR T cells, usually manifests as fever and flu-like symptoms, although severe CRS can present as multiorgan failure, capillary leak syndrome, and hemodynamic instability; patients may show laboratory evidence of disseminated intravascular coagulation or overlap with macrophage activation syndrome/hemophagocytic lymphohistiocytosis.[10]

ICANS can manifest as encephalopathy, headache, tremor, ataxia, facial nerve palsy, seizures, and, in rare cases, fatal fulminant cerebral edema.[11,12] Incidence, severity, and timing of ICANS may vary by CAR T-cell infusion dose, lymphodepletion regimen, and patient age, among other clinical factors.[13] Although most patients with ICANS have history of CRS,[12] ICANS and CRS can occur independently of each other,[11]

suggesting that these might be related but distinct phenomenon.

The mechanism underlying ICANS is still being elucidated, but recent advances have implicated a central role of circulating cytokines, endothelial activation, and blood-brain barrier (BBB) dysfunction. Histologic examination of animal models and postmortem human brain tissue has provided invaluable insight into the pathophysiology of this disorder. The authors now discuss the putative mechanism of ICANS.

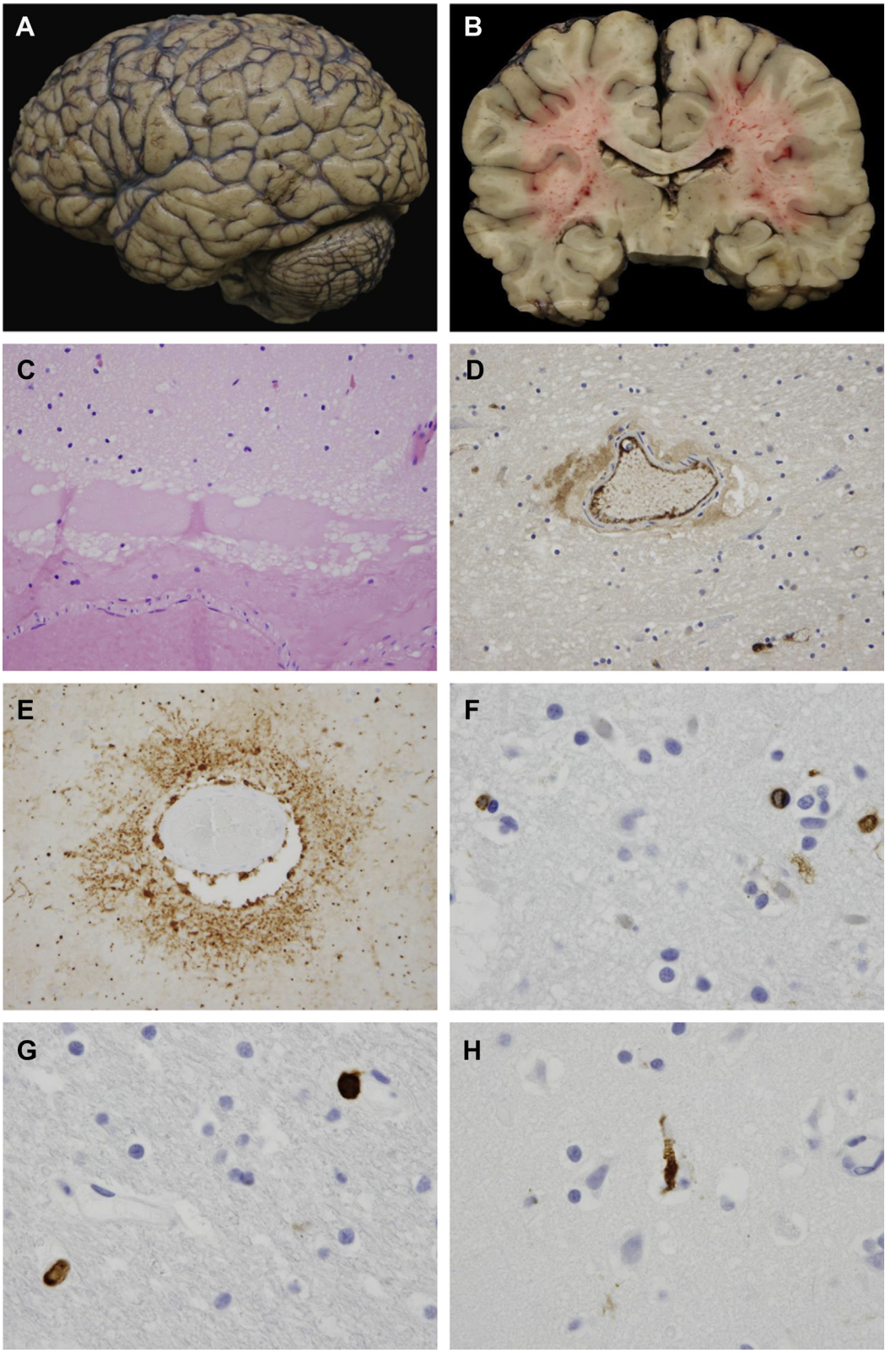
Elevated circulating cytokines have been linked to ICANS. As previously mentioned, most of the patients with severe ICANS will have history of CRS,[3,7,8,12–14] and increased levels of circulating cytokines such as interkeukin (IL) 6, IL-2, IL-10, IL-15, interferon (IFN) γ, tumor necrosis factor alpha (TNFα), and granulocyte-macrophage colony-stimulating factor (CSF) have been correlated with the presence or severity of ICANS.[5,7,8,13,14] Elevated serum cytokines have also been shown in an anti-CD20 CAR T-cell nonhuman primate model demonstrating neurotoxicity.[15] Recent evidence from CAR T-cell mouse models[16,17] suggests that monocytes/macrophages (rather than CAR T cells) are the primary source of proinflammatory cytokines that account for the severity of CRS and ICANS. Macrophage depletion can abrogate CRS-related toxicity and release of IL-6.[18]

Elevated circulating cytokines may promote ICANS through aberrant endothelial activation and BBB dysfunction. Exposure to proinflammatory cytokines shifts endothelial cells from a quiescent to activated phenotype, a process that is mediated by the angiopoietin (ANG)–TIE2 system.[19,20] On activation, endothelial cells release ANG2 and von Willebrand factor (vWF) from storage granules called Weibel-Palade bodies into circulation.[19,21] ANG2 antagonizes ANG1-TIE2 signaling, disrupting endothelial quiescence and maturation, promoting leukocyte transmigration, and increasing BBB permeability via internalization of proteins necessarily for BBB integrity, such as tight junctions and adherens junctions.[19,22] Patients with severe ICANS show increased serum ANG2, reduced serum ANG1, and/or higher ANG2:ANG1 ratios,[8,13] providing biomarker evidence for endothelial activation. Moreover, patients with severe ICANS have elevated serum vWF and evidence of consumptive coagulopathy,[8,13] also in keeping with endothelial activation. Increased BBB permeability is supported by elevated CSF protein, CSF/serum albumin quotient, and proinflammatory cytokines in the CSF of patients with ICANS.[8,13] Elevated proinflammatory cytokines in the CSF have also been demonstrated in a nonhuman primate model.[15]

Postmortem neuropathologic studies performed on CAR T-cell patients and animal models provide corroborating evidence for endothelial activation and BBB dysfunction. Gust and colleagues[13] reported platelet microthrombi, intravascular vWF binding, endothelial disruption, erythrocyte extravasation, microhemorrhages, and microinfarcts accompanied by vascular fibrinoid necrosis in a patient with severe ICANS who died 13 days after CAR T-cell infusion; platelet microthrombi were also identified in a second patient with history of severe ICANS. A case report of a patient who died from fulminant cerebral edema 4 days after CAR T-cell infusion (**Fig. 1**A, B) described expansion of the perivascular spaces (**Fig. 1**C) with fibrin and factor VIIIA-positive fluid (**Fig. 1**D), edematous, vacuolated white matter, and clasmatodendrosis (ie, beading and fragmentation of astrocytic processes), which was accentuated around blood vessels, consistent with BBB disruption (**Fig. 1**E).[23] A nonhuman primate model showed rare foci of perivascular edema during peak neurotoxicity.[15]

In addition, most histologic descriptions of ICANS comment on an inflammatory cell infiltrate involving central nervous system (CNS) tissue, compatible with altered BBB integrity. Descriptions from human and animal models include perivascular CD8+ lymphocytes, with the majority composed of CAR T cells[13]; intraparenchymal CD8+ T cells and abundant macrophages in degenerated white matter[6]; multifocal meningitis and perivascular and intraparenchymal T cells (both CAR T cells and non-CAR T cells)[15]; thickening of the meninges with infiltration of the subarachnoid space by macrophages[17]; and perivascular macrophages with only rare scattered lymphocytes (**Fig. 1**F, G) and no identifiable CAR T cells.[23] The variability in the number, composition, and distribution of inflammatory cells in the CNS raises questions about their role in the development of ICANS, particularly the role of infiltrating CAR T cells.

Cytokines may be relatively enriched in the CSF compared with peripheral blood during severe ICANS,[8,15,24] suggesting that there might be intracranial sources of cytokine production. Microglia are a possible candidate for intracranial production of cytokines,[25] and postmortem studies of patients with history of ICANS have consistently shown prominent and/or reactive microglia[6,13,23] (**Fig. 1**H). However, activated microglia or increased numbers of microglia have not been described in CAR T-cell animal models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demonstrating neurotoxicity,[15,17] with one mouse model actually showing a reduction in the total number of Tmem119+ microglia compared with controls.[26] Other possible intracranial sources of cytokine production include pericytes,[13,27] endothelial cells,[22,28] and astrocytes.[29,30] Notably, release of cytokines by intracranial cell populations may further increase BBB permeability and exposure to circulating proinflammatory cytokines, resulting in a positive feedback loop that exacerbates BBB dysregulation.

Alterations of the cellular milieu of the CNS due to increased BBB permeability and exposure to elevated cytokines may be injurious to astrocytes and neurons. Elevation of CSF levels of S100 calcium-binding protein B and glial fibrillary acidic protein (GFAP) in patients with ICANS[14] and perivascular clasmatodendrosis in a postmortem examination of a patient with fatal CAR T-cell cerebral edema[23] suggest astrocyte injury. Diffuse gliosis, reflective of general CNS injury, has been reported.[6] Increased CSF concentrations of N-methyl-D-aspartate receptor agonists quinolinic acid and glutamate, compatible with excitotoxicity, have also been shown in patients with ICANS.[8] Exposure to excitotoxic agents may result in neuronal death.[31] Neuronal loss has been identified in the postmortem examination of one patient with history of optic atrophy and follicular lymphoma treated with CAR T-cell therapy and fludarabine lymphodepletion,[6] although the pathogenesis underlying this patient's neuronal loss is unclear and likely multifactorial.

Chronic changes associated with CAR T-cell therapy may include cortical atrophy, gliosis of the gray and white matter (particularly prominent in the subpial region), persistent microglial activation, widened perivascular spaces with hemosiderin-laden macrophages, and abundant corpora amylacea.[14]

Importantly, there does not seem to be overt, specific neuropathology associated with CRS in the absence of ICANS in individuals given CAR T-cell therapy. However, this observation is based on rare published descriptions. The gross and microscopic neuropathologic examination of one patient with severe CRS, but no history of ICANS, was described as grossly (**Fig. 2**A, B) and microscopically (**Fig. 2**C, D) unremarkable.[12] In a CAR T-cell mouse model showing CRS without neurotoxicity, there was no cerebral edema, gliosis, hemorrhage, or necrosis.[16]

To summarize, although the precise mechanism underlying ICANS is still being elucidated, there is an emerging model in which activation and expansion of CAR T cells result in cytokine release, particularly from monocytes/macrophages, inducing endothelial cell activation and BBB dysfunction. Cytokines can then cross the permeable BBB, which may also potentiate release of additional cytokines from pericytes, endothelial cells, astrocytes, and/or microglia in a positive feedback loop, further exacerbating BBB dysfunction. Exposure to cytokines may initiate cascades of events that are injurious to astrocytes and neurons. Neuropathologic examination of patients and animal models has shown a broad spectrum of histologic changes in association with ICANS, including perivascular fluid extravasation, platelet microthrombi, hemorrhage, microinfarcts, clasmatodendrosis, gliosis, microglial activation, and infiltration of the brain parenchyma, subarachnoid space, meninges, and/or perivascular spaces by inflammatory cells, including CAR T cells.

A diverse set of disorders may have histologic features that overlap with ICANS: posterior reversible encephalopathy syndrome (PRES) (which can be secondary to autoimmune disorders, hypertension, sepsis, amphetamine, and myriad medications including vascular endothelial growth factor inhibitors), viral encephalitis, cerebral malaria, acute necrotizing encephalopathy, acute hemorrhagic encephalopathy, and toxin exposure (eg, lead), among other entities. Correlation with clinical history and laboratory findings is essential for this histologic differential, especially because the microscopic features of ICANS are nonspecific and based on a limited number of published reports.

Fig. 1. Gross and microscopic neuropathologic findings in an anti-CD19 CAR T-cell patient with fulminant cerebral edema and severe ICANS. (*A*) Grossly edematous brain with (*B*) narrowed ventricles. There was (*C*) expansion of the perivascular spaces (H&E, 400x) with fibrin (not shown) and (*D*) factor-VIIIA-positive material (400x), consistent with fluid extravasation. (*E*) Clasmatodendrosis was particularly notable around blood vessels (GFAP, 400x), which suggests astrocyte injury and BBB dysfunction. (*F*) Admixed inflammatory cells were present (leukocyte common antigen stain, 1000x), including (*G*) scattered T cells (CD3, 1000x) and (*H*) activated rod microglia (CD68, 1000x). ICANS, immune effector cell–associated neurotoxicity syndrome.

CONVENTIONAL CHEMOTHERAPY

Highlights

Clinical:

- Neurologic adverse effects of conventional chemotherapy include encephalopathy, headache, neurovascular complications, seizures, movement disorders, pancerebellar syndrome, "stroke-like" syndrome, posterior reversible encephalopathy syndrome, chemotherapy-related cognitive impairment (CRCI), peripheral neuropathy, myopathy, and dysfunction of the enteric nervous system.
- Chemotherapy-induced leukoencephalopathy is particularly associated with methotrexate (although it has been observed with other chemotherapeutics), concurrent brain radiation, and intrathecal or intraventricular administration of chemotherapy.
- CRCI affects approximately 15% to 25% of patients, involves multiple cognitive domains, and may persist for up to 20 years after cessation of treatment in a subset of patients.

Putative Mechanism of Neurotoxicity Associated with Chemotherapy:

- Chemotherapy-induced leukoencephalopathy: the pathophysiology is unclear, but chemotherapeutic agents have a direct cytotoxic effect on central nervous system (CNS) progenitor cells and oligodendrocytes and impair the self-renewal potential of oligodendrocyte precursors at sublethal concentrations. Oxidative stress may also be contributory.
- CRCI: multiple implicated mechanisms include elevated proinflammatory cytokines, reactive oxygen species/oxidative stress, DNA damage, blood-brain barrier dysfunction, direct effects of chemotherapy on CNS cells, neuroinflammation, and dysmyelination.

Histology:

- Chemotherapy-induced leukoencephalopathy: foci of demyelination and necrosis, axonal swellings, myelin pallor, white matter vacuolization/spongiosis, edema, and gliosis, with a generally limited inflammatory cell reaction.
- CRCI: reactive astrocytes, activated microglia, reduced CNS progenitors, and oligodendrocytes.

Histologic Differential:

- Chemotherapy-induced leukoencephalopathy: leukoencephalopathy from another inciting cause (eg, hypoxia, radiation, other therapeutic medication, metabolic disorder, AIDS, drugs of abuse, or environmental toxins), genetic leukodystrophy, demyelinating disorders, and infection (eg, JC virus).

Chemotherapeutic agents can be divided into several major classes based on mechanism of action and derivation, including alkylating agents, anthracyclines, antimetabolites, plant alkaloids, and topoisomerase inhibitors. Chemotherapy is associated with a range of adverse effects involving the CNS (eg, encephalopathy, headache, neurovascular complications, seizures, movement disorders, pancerebellar syndrome, "stroke-like" syndrome, PRES, and chemotherapy-related cognitive impairment [CRCI]), peripheral nervous system (eg, peripheral neuropathy), musculoskeletal system (eg, myopathy), and enteric nervous system. These adverse neurologic effects are clinically significant, can be dose-limiting, and may prompt cessation of therapy.

White matter damage following chemotherapy treatment (with or without radiation therapy) may manifest in severity from progressive and oftentimes fatal disseminated necrotizing leukoencephalopathy (DNL)[32] to transient, clinically asymptomatic lesions.[33] Although chemotherapy-induced leukoencephalopathy is commonly associated with methotrexate,[32,34,35] it has also been observed with fludarabine, carmustine, vincristine, cyclophosphamide, doxorubicin, 5-fluoruoracil, and cisplatin, among other chemotherapeutic agents.[32,35–37] Intrathecal or intraventricular administration of chemotherapeutic agents and/or concurrent brain radiation may predispose patients to developing leukoencephalopathy.[32,34,35]

There is variability in the histologic descriptions of chemotherapy-induced leukoencephalopathy.[32,34–37] The prominent features of DNL[32] are multiple foci of demyelination and necrosis, often confluent and sometimes markedly extensive, with characteristic axonal swellings (composed of mitochondria, microfilaments, autophagic vacuoles, and calcifications) that are found within and adjacent to the foci of necrosis. Spongiosis, edema, and reactive astrocytes may be observed near the areas of demyelination and necrosis. Fibrinoid vascular necrosis and fibrin extravasation can be present but are most likely attributable to concurrent brain radiation. The accompanying inflammatory cell reaction is generally very limited. However, there may be abundant periodic acid–Schiff-positive macrophages.[36] The extent of myelin loss, white matter vacuolization, edema, gliosis, and

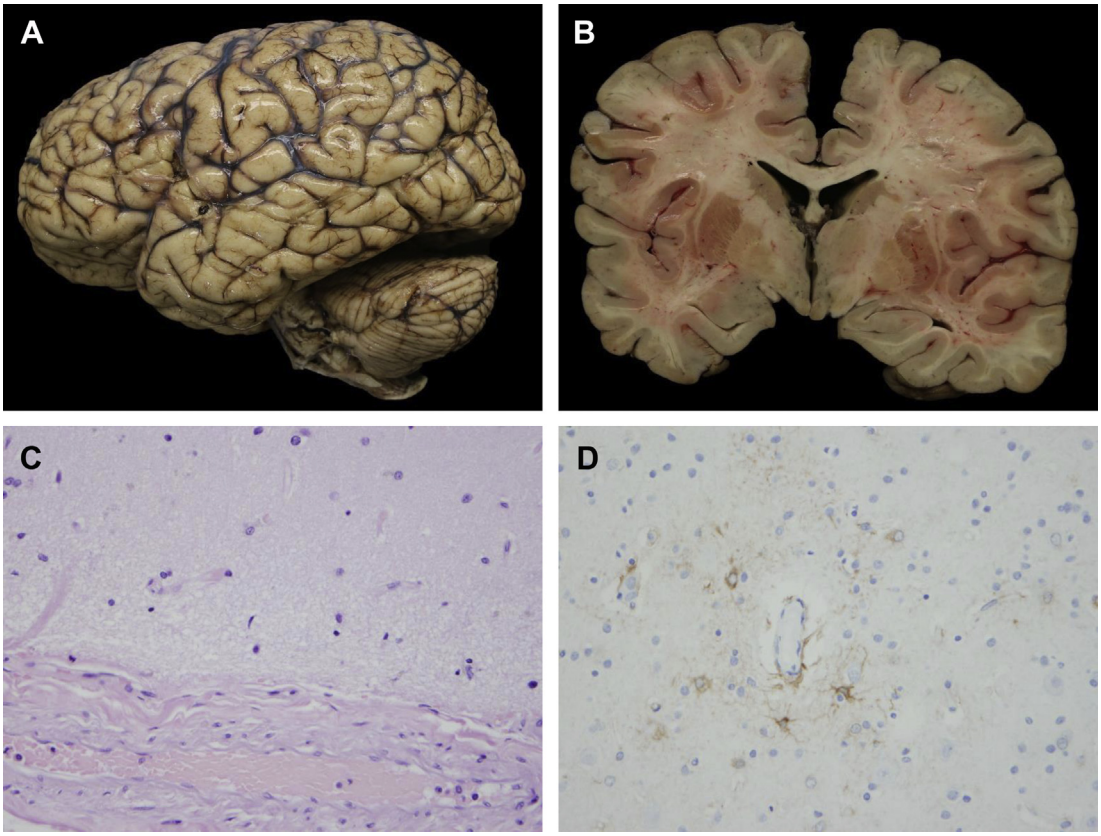

Fig. 2. Gross and microscopic neuropathologic findings in an anti-CD19 CAR T-cell patient with CRS but no history of ICANS. (*A*, *B*) Grossly unremarkable brain with (*C*) no specific microscopic pathologic change (H&E, 400x) and (*D*) minimal gliosis (GFAP, 400x).CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

frequency of axonal swellings in chemotherapy-induced leukoencephalopathy is highly variable.[36–38] An example of the histologic changes seen with a case of chemotherapy-induced leukoencephalopathy is provided in **Fig. 3**.

The histologic differential for chemotherapy-induced leukoencephalopathy is broad and includes leukoencephalopathy due to hypoxia, radiation, other therapeutic medication, metabolic disorder, AIDS, JC virus, drugs of abuse, or

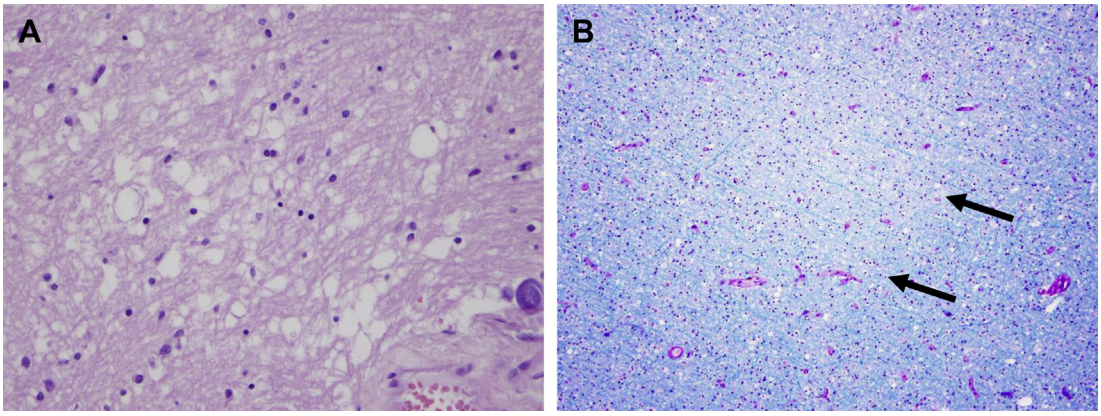

Fig. 3. Leukoencephalopathy in a patient recently treated with cyclophosphamide. Postmortem neuropathology was notable for (*A*) vacuolization of the white matter (H&E, 400x) with (*B*) subtle patchy loss of myelin (*arrows*, LFB/PAS, 100X).

environmental toxins; genetic leukodystrophy; and demyelinating disorders. Clinical history and laboratory findings will narrow the differential, as the histology can be nonspecific.

The pathophysiology of chemotherapy-induced leukoencephalopathy is unclear, but direct cytotoxicity of chemotherapy to CNS progenitor cells and oligodendrocytes is plausible. Neuronal and oligodendrocyte precursors, as well as oligodendrocytes, are extremely sensitive to multiple chemotherapeutic agents, even at low subtherapeutic concentrations.[39,40] Carmustine, lomustine, temozolomide, cisplatin, paclitaxel, and 5-fluororacil have all been shown to cross the BBB.[41–44] It is also conceivable that systemically administered chemotherapeutic agents with poor BBB penetrance may accumulate at sufficient concentrations in the CNS to be lethal to CNS precursor cells and oligodendrocytes, particularly when there is compromise of BBB integrity as can be observed following brain radiation. In addition to their direct cytotoxic effects, chemotherapies may induce differentiation and persistent alterations in the self-renewal potential of oligodendrocyte precursors, potentially resulting in delayed myelination damage and impaired ability to repair subsequent white matter injury.[39,40,45] The presence of axonal swellings suggests impaired axonal transport, which may be mediated by direct action of certain chemotherapies on microtubules[46] or by oxidative stress/mitochondrial dysfunction.[47]

An increasingly recognized adverse neurologic effect of chemotherapy is the development of cognitive deficits (CRCI, sometimes referred to as “chemobrain” or “chemofog”). CRCI is observed in a subset of chemotherapy patients, typically cited in the range of 15% to 25%,[48] although the incidence may approach 80%.[49] Cognitive domains frequently impaired include memory, attention, executive function, and processing speed.[50] Although the extent of cognitive impairment may be mild to moderate[51] and vary depending on study design, patient characteristics, control group, cognitive domains examined, and whether baseline cognition is assessed,[52,53] these deficits are nevertheless associated with significant patient morbidity. Patients’ perceived cognitive impairment may contribute to worse qualitative work-related outcomes[54] and impaired quality of life and daily functioning.[55] The incidence and severity of CRCI is generally thought to abate over time, but some patients have cognitive deficits that persist for up to 20 years after the last dose of chemotherapy,[56] and other patients only develop cognitive problems over a year after treatment cessation.[57] Radiologic studies have shown volumetric brain loss,[58,59] altered levels of brain activation during cognitive tasks,[60,61] evidence of impaired global brain network organization,[62] and changes to white matter integrity[63,64] following chemotherapy treatment. Older age, lower cognitive reserve, ApoE status, and other clinical factors may predispose patients to developing CRCI.[65,66]

The pathophysiology underlying CRCI is not fully elucidated, but data support several complementary mechanisms, including (1) elevated proinflammatory cytokines, reactive oxygen species (ROS), oxidative stress, and DNA damage; (2) BBB dysfunction; (3) direct effects of chemotherapy on CNS cells; (4) neuroinflammation; (5) and dysmyelination. Many chemotherapeutic agents function therapeutically by promoting oxidative stress and DNA damage.[67] This is done through several pathways such as generation of superoxide radicals and ROS.[68] Patients treated with chemotherapy have increased circulating ROS.[69] Chemotherapy is also associated with elevated peripheral proinflammatory cytokines,[70–73] such as IL-6 and TNFα, that are released from inflammatory cells,[74] tumor cells,[75] and nonneoplastic tissue including gastrointestinal mucosa.[76] Peripheral ROS and proinflammatory cytokines can alter the permeability of the BBB,[77] potentially allowing greater concentrations of chemotherapeutic agents and peripheral cytokines to cross the BBB into the brain, which has several important sequelae. Firstly, the direct effects of chemotherapy on CNS progenitor cells and oligodendrocytes[39,40] may contribute not only to white matter damage but also to impaired hippocampal neurogenesis and memory deficits.[39,78–80] Secondly, circulating proinflammatory cytokines and ROS can instigate neuroinflammation, leading to increased intracranial production of cytokines, mitochondrial dysfunction,[81] oxidative stress,[82] and neuron apoptosis.[83] Neuroinflammation also impairs hippocampal neurogenesis.[84] Data from Gibson and colleagues[85] support a central role of microglia in the cognitive deficits, induction of astrocyte reactivity, altered oligodendrocyte lineage dynamics, and reduced myelin sheath thickness in their mouse model of CRCI.

SUMMARY

Iatrogenic neuropathology secondary to systemic antineoplastic agents such as CAR T-cell therapy and conventional chemotherapy may result in significant patient morbidity and mortality. Understanding the pathophysiology underlying these adverse effects not only offers insight into potential ameliorating therapies but also sheds light on the regulation of the neurovascular unit and how

circulating cytokines and other substances may either impair or directly cross the BBB, initiating cascades of deleterious, sometimes chronic, effects potentially mediated by cell populations intrinsic to the CNS. These pathways may be relevant to neurodegeneration and senescence of the aging brain.

DISCLOSURE

The authors have no sources of funding to disclose. The authors declare no conflict of interest.

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