Good Gone Bad: Complications of Chemotherapy, Immunotherapy and Radiotherapy on the CNS

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Learning Objectives

• Classify major treatment complications into four main categories: Chemotherapy, Immunotherapy, Radiotherapy, and Miscellaneous
• Demonstrate imaging features unique to each therapy side effect or toxicity within each category using illustrative case examples
• Understanding important mechanisms accounting for toxicities
Chemotherapeutic Agents
Asymptomatic patients imaged during treatment have confluent deep white matter T2/FLAIR hyperintensities.

Symptomatic patients may have atypical localization of T2/FLAIR hyperintensities e.g. thalamus, basal ganglia, cerebellum and brainstem. Acute to subacute leukoencephalopathy demonstrates restricted diffusion before T2/FLAIR signal abnormality.

Increased T2/FLAIR hyperintensities in both periventricular and deep white matter regions *with* associated diffusion restriction. No enhancement or susceptibility artifact.
Chronic methotrexate-induced leukoencephalopathy

Symmetric confluent areas of T2/FLAIR hyperintensities *without* diffusion restriction or enhancement within the periventricular and deep white matter
Methotrexate-induced Disseminated Necrotizing Leukoencephalopathy (DNL)

- More severe and often fatal form of progressive disease originally described in children with metastatic meningeal acute lymphoblastic lymphoma (ALL)

Numerous diffusion restricting, enhancing lesions throughout the brain with associated edema and mild mass effect. Presence of low signal foci within the T2/FLAIR abnormalities and contrast enhancement are more suggestive of DNL indicating a more fulminant disease process.
Chemotherapy induced myelopathy

- Methotrexate and cytarabine (Ara-C) are the most common causative intrathecal agents.

- Etiology remains unclear; the neurotoxicity may be result of aseptic meningitis incited by preservative used in the diluent or as in the case of methotrexate, it may be result of local depletion of folate secondary to methotrexate.

Multiple patchy or long segment T2/STIR hyperintensities, cord expansion with patchy areas of intramedullary enhancement.
Immunotherapeutic Agents
Tacrolimus-induced Myelopathy

- Used in solid organ transplant patients
- Implicated in sensorimotor demyelinating polyneuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP)
- Risk of developing toxicity may be reduced by switching to Everlimus

Non-enhancing T2 hyperintensities within the spinal cord of varying lengths and extent.
Tacrolimus-related Optic Neuropathy

- Patients present with varying degrees of acute to subacute painless vision loss
- Tends to be bilateral
- Pathogenesis involves increase in thromboxane A2 levels causing vasoconstriction with resultant ischemia of optic nerves, direct toxicity to myelin surrounding optic nerves due to lipophilic nature, and axonal edema

T2/FLAIR hyperintensity and enhancement involving the optic nerve and chiasm
Immune reconstitution inflammatory syndrome (IRIS-PML)

• Paradoxical deterioration of pre-existing illness following abrupt improvement in an individual's immune function

• Classically seen in HIV/AIDS patients following initiation of highly active anti-retroviral therapy (HAART) and diseases treated with immunomodulation (e.g. Natalizumab-associated progressive multifocal leukoencephalopathy IRIS in multiple sclerosis)

• Clinically, symptoms typically develop within 60 days following initiation of HAART, and mimic worsening of the underlying condition, despite rising CD4 counts and a falling viral load

• Imaging features either reflect the imaging appearances of the underlying disease, may mimic worsening of the underlying condition, or be atypical. Enhancing masses gain mass effect rapidly. Enhancement is variable and may appear bizarre

• Differentials include non-IRIS associated opportunistic infection and CNS lymphoma

• Treatment is with corticosteroid therapy alongside HAART. Fatal cases < 5%
Immune reconstitution inflammatory syndrome (IRIS-PML)

Similar distribution with slightly increased size of T2/FLAIR hyperintensities, T1 hypointensities, new diffusion restriction and new areas of subtle enhancement
Immune reconstitution inflammatory syndrome-Progressive Multifocal Leukoencephalopathy (IRIS-PML)

Similar distribution of intramedullary demyelinating lesion with slightly increased size and extent of enhancement
Rituximab-associated Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating infection of oligodendrocytes caused by reactivation of the JC virus in patients with compromised and recovering immune system function
- This is in contradistinction to more symmetrical involvement and sparing of the U-fibers in HIV encephalopathy
- No enhancement, no mass effect

Multilobar non-enhancing asymmetric T1 hypointensities, T2/FLAIR hyperintensities and confluent hypodensities, more prominent within periventricular and subcortical regions involving of U-fibers

Diffusion restriction at the leading edge may be present
Bevacizumab (Avastin) induced anterior nasal septal perforation

• Rare complication of systemic therapy

• Time to presentation around 20 weeks

• Mechanism of toxicity unclear; likely multifactorial, including inhibition of VEGF-A, resulting in reduction in angiogenesis and mucositis from bevacizumab itself
Mycophenolate induced Atypical Posterior Reversible Encephalopathy Syndrome (PRES)

- Atypical PRES has predilection for anterior circulation, cortical location, unilaterality, hemorrhage, diffusion restriction and enhancement

Multifocal regions of FLAIR hyperintensities within the deep white matter with petechial hemorrhage and diffusion restriction from atypical PRES
Ipilimumab induced hypophysitis

5/26/2016

Pituitary hyperplasia with mild superior displacement of the thickened infundibulum which remains at midline.

9/21/2016

Complete resolution of pituitary hyperplasia and thickening of the infundibulum with drug cessation. Findings are consistent with ipilimumab hypophysitis.
Bevacizumab (Avastin) neurotoxicity

- Hypothesized that bevacizumab use following radiotherapy to the CNS may inhibit vascular endothelial growth factor-dependent repair of normal neural tissue, and thus may increase the risk of late radiation neurotoxicity.

Foci of intrinsic T1 hyperintensity and diffusion restriction involving the white matter.

Confluent T1 hypointensity and T2/FLAIR hyperintensity lined by intrinsic T1 gyral hyperintensities.
Radiation induced neurotoxicity
Radiation induced cavernous malformations

• Risk factor is childhood CNS irradiation

• CNS vascular lesions composed of thin-walled, dilated capillary spaces with no intervening brain tissue

• Pathogenesis involves proliferative vasculopathy triggered by radiation injury to cerebral microcirculation

T1 heterogeneous, T2 heterogeneous lesions with hemosiderin rim and corresponding susceptibility artifact
Radiation induced glandular and muscular atrophy

- Usually seen in necks that have been treated with radiation and chemotherapy to avert a radical neck dissection for head and neck cancers

Fatty replacement of bilateral submandibular and right parotid glands and diminutive appearing right sternocleidomastoid muscle
Radiation induced myelopathy

- May present as a transient early or delayed reaction
- Transient reaction develops 3-4 months after treatment and spontaneously resolves over 3-6 months without therapy. Attributed to transient demyelination, patients present with Lhermitte's sign
- Irreversible myelopathy occurs after 6-12 months due to demyelination and white matter necrosis
- A diagnosis of exclusion and no known consistently effective treatment exists

MRI findings include swelling of the spinal cord with T2 hyperintensity, T1 hypointensity, with or without enhancement
Radiation necrosis

• Occurs greater than 6 months following radiotherapy
• Restricted diffusion with an elevated rCBV favor recurrent tumor than radiation necrosis
• Knowledge of the radiation treatment plan, amount of brain tissue included in the radiation port, type of radiation, location of primary malignancy, and amount of time elapsed since radiation therapy is extremely important in determining whether the imaging abnormality represents radiation necrosis or recurrent tumor

MRI findings include decreased relative cerebral blood volume (rCBV) with or without restricted diffusion and enhancement
Radiation induced cerebral atrophy

- Natural course remains unclear and generally regarded as a progressive, irreversible process

- White matter lesions develop first, followed by contrast-enhanced lesions, which tend to become necrotic with increasing size. Least frequent manifestations are cysts, arising in late stages

- Atrophy becomes obvious 2-3 months after radiation therapy in more than half patients. Mental and neurologic deterioration correlate with severity of atrophy

- Risk factors include large target field or whole brain irradiation and advanced patient age
Radiation induced leukoencephalopathy

- Well-described late sequelae of whole-brain radiation therapy which remains common practice for cerebral metastases, either as monotherapy or in conjunction with surgery or stereotactic radiosurgery
- Defined clinically by neurocognitive changes and imaging findings

Deep and periventricular confluent white matter hyperintensities on T2/FLAIR in the absence of focal lesions and typical sparing of U-fibers
Radiation induced vasculopathy/Moya-Moya syndrome

- Progressive multifocal steno-occlusive vasculopathy at terminal portions of the bilateral internal carotid arteries and their proximal branches with prominent collateral artery formation

- Small abnormal net-like vessels proliferate giving the characteristic “puff of smoke” appearance
Radiation induced mineralizing microangiopathy

- A non-inflammatory microangiopathy seen mostly after irradiation (even with relatively low doses such as 10 Gy) or intrathecal methotrexate instillation
- Mainly affects the small cerebral vessels especially the Aa. Perforantes, which subsequently obliterate
- Histological examination exhibits calcifications, mucopolysaccharide and necrotic deposits in and around the small cerebral vessels

After a mean lag of about 10 months, calcifications appear in the basal ganglia, thalami, and white matter
Radiation induced osteonecrosis of the jaw

• Risk factors: primary bone surgery during tumor resection, tumors located in the oral cavity (higher dose), sex (females < risk, males > risk/nicotine use), dentition (dentulous vs. edentulous, entry point for pathogenic germs), and chemotherapy (free radicals)

• Pathogenesis includes irradiation-induced fibrosis with histopathological phases like those of chronic wounds

• Susceptibility of the mandible is because the blood supply is limited to a single functional terminal artery. The facial artery does not produce enough collaterals to compensate for loss of blood supply occurring after fibrosis of the inferior alveolar artery

Mottled appearance of the mandibles with absent third right mandibular molar and erosion along the right mandibular alveolar ridge
Radiation induced optic neuropathy

- Exclusive iatrogenic phenomenon
- Delayed radionecrosis of the anterior visual pathways, which develops within months to years after external cranial irradiation. Causes severe and irreversible vision loss
- Pathogenesis involves direct damage to macromolecules and formation of free peroxide and superoxide radicals in the presence of oxygen
- Volume loss with diminutive appearing nerve may be evident
- Enlargement of the optic nerve may be explained by hemorrhage due to radiation-induced vasculopathy

Characterized by T2/FLAIR hyperintensities with linear enhancement
Radiation induced SMART syndrome (Stroke-like migraine attacks after radiation therapy)

- Uncommon delayed complication presenting years after radiation therapy with migraine-like headache, seizures, subacute stroke-like episodes, hemiplegia, aphasia, and hemianopia
- Self-limiting and gradually resolves over the course of several weeks

T1 hypointensity (cortical hyperintensity can be seen if associated with cortical laminar necrosis from prior events), T2/FLAIR hyperintensity with cortical thickening, variable diffusion restriction and prominent unilateral gyriform leptomeningeal and cortical enhancement
Miscellaneous
Gadolinium Deposition Disease

- Gadolinium is toxic but considered safe when chelated to molecules such as DTPA. The molecular structure of the contrast agent plays a role in gadolinium retention.
- Two structurally distinct classes of gadolinium-based contrast agents (GBCA) are identified: linear and macrocyclic.
- With the macrocyclic structure, gadolinium is bound more tightly to the chelating agent and is less likely to be released as free gadolinium, thus less toxic and less likely to be deposited.
- With the linear structure, gadolinium is bound more loosely to the chelating agent and is more likely to be released as free gadolinium, thus more toxic and more likely to be deposited.

Non-enhancing T1 hyperintensities and T2/FLAIR hypointensities with susceptibility artifact within globus pallidi and dentate nuclei.
MRI changes in Total Parenteral Nutrition (TPN)

- Presents with hypermagnesemia and clinically with liver and nervous system disorders
- Secondary to deposition of the trace element manganese
- Manganese has a propensity for basal ganglia structures, including globi pallidi, substantia nigra, and subthalamic nuclei. Chronic deposition results in dopamine depletion and development of parkinsonian-type syndromes
- After cessation of TPN, imaging findings can completely disappear; however, clinical symptoms may persist

Increased deposition appears as hyperattenuation on CT and abnormally high T1 signal intensity
Pseudotumor cerebri from Vitamin A toxicity

Typical findings include flattening of bilateral optic discs, intraocular protrusion with mild enhancement of the optic nerve heads and prominent subarachnoid spaces surrounding the tortuous optic nerves. Bilateral low-lying cerebellar tonsils with mild crowding of the foramen magnum. Mildly slit-like ventricles and partially empty sella.

- Etiologies include endocrine conditions, medications (doxycycline, Vitamin A), chronic renal failure, systemic lupus erythematosus and rarely, dural venous stenosis/web.
Bisphosphonate induced osteonecrosis of the jaw

Characterized by non-healing exposed bone in the maxillofacial region. Unclear etiology, likely multifactorial and primarily a clinical diagnosis. Tissue sampling may exacerbate the process, thus avoided. Imaging appearance is variable and includes sclerotic, lytic, or mixed lesions with possible periosteal reaction, pathologic fractures, and extension to soft tissues. Knowledge of this entity is important, to include it in differentials with histories of bisphosphonate therapy without jaw irradiation, to avoid potentially harmful biopsies.

Multiple lucencies with underlying lytic destruction of the left mandibular body and ramus
Cytotoxic Lesion Of the Corpus Callosum (CLOCC)

9/20/2017

5/10/2018

Non-enhancing diffusion restriction and FLAIR hyperintense cytotoxic edema within the expanded splenium corpus callosum. Reported etiologies include seizures (with or without antiepileptic medications), metabolic disturbances, CNS infections and malignancies, drugs and toxins. Complete reversibility is most likely outcome after resolution of inciting event without residual signal abnormality or volume change.
Cerebellar and vermian degeneration from Phenytoin treatment

- CT and MRI demonstrate a small sized cerebellum and vermis
- PET/CT/MRI demonstrate symmetrically decreased FDG uptake within the cerebellar hemispheres and vermis
- Seen in cases of long-standing treatment with phenytoin and/or longstanding epilepsy
Metronidazole central nervous system neurotoxicity

- Commonly administered antibiotic for CNS infections such as bacterial abscess
- CNS involvement is almost always bilateral and symmetric
- Uncommon lesion locations include inferior olivary nucleus of the medulla and white matter of the cerebral hemispheres
- Resolves upon discontinuation of the medication

Non-enhancing, diffusion restricting T2/FLAIR hyperintensities involving the posterior limbs of the internal capsules, midbrain, pons and dentate nuclei
Normal saline induced osmotic demyelination syndrome

- Reversible acute demyelination seen in the setting of osmotic changes, typically with rapid correction of hyponatremia.
- It replaces the previous term central pontine myelinolysis, as extrapontine structures (ventrolateral thalami, basal ganglia, caudate nuclei, internal, external and extreme capsules, gray white matter junction and splenium corpus callosum) can also be affected, previously known as extrapontine myelinolysis.
- Earliest abnormality is DWI within 24 hours of quadriplegia in a trident appearance within the central pons, sparing the periphery and corticospinal tracts, followed by T2/FLAIR hyperintensity and T1 hypointensity (which may lag by 2 weeks). Rarely, there may be associated enhancement.
Vigabatrin induced neurotoxicity

- Antiepileptic drug for treatment of infantile spasms
- Affect patients < 2 years and more likely children < 12 months
- MRI changes appear after five weeks to six months and remit completely after three months, even without discontinuation
- Alterations are dose dependent but do not have a relation to the duration of treatment
- Patients with infantile spasms treated with other drugs like ACTH or prednisone, do not exhibit MRI signal changes

Confluent foci of reversible T2 hyperintensities and diffusion restriction in the basal ganglia, thalami, dorsal brainstem and dentate nuclei; globi pallidi being the more frequently involved
References


References


