Iatrogenic brain damage

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Learning objectives

To illustrate the spectrum of iatrogenic damage in the brain parenchyma after surgery, radiotherapy, chemotherapy and immunosuppressive therapy.

To highlight the importance of various MR modalities in the differentiation between radiation necrosis and recurrent neoplastic infiltration.
Background

Damage of the central nervous system (CNS), as a result of treatment complications, may present as acute, subacute and chronic processes. Apart from brain surgery, radiotherapy, chemotherapy and immunosuppressive therapy are the most common causes of CNS iatrogenic damage. Localization and extension of pathological damage to the CNS correlate with the type and severity of clinical symptoms.

This exhibit briefly describes and illustrates the spectrum of MR findings of the most common causes of iatrogenic brain damage, with a particular emphasis on the distinction between tumor recurrence and radiation necrosis.
Findings and procedure details

Gliosis of brain parenchyma after surgery, extensive demyelination of white matter caused by intrathecal administration of chemotherapeutic agents, posterior reversible encephalopathy syndrome as well as brain radiation necrosis, were the most frequently observed iatrogenic lesions.

Magnetic resonance spectroscopy (MRS) and MR perfusion-weighted imaging (PWI) were performed in the differentiation of iatrogenic sequels and recurrent neoplastic process.

1. Gliosis of brain parenchyma as a result of brain surgery (Fig. 1 on page 8)

Gliosis is the universal response of the CNS to tissue injury and occurs as a result of many acute conditions (trauma, ischemia, stroke…), as well as in a wide variety of CNS pathologies (multiple sclerosis, vasculitis, amyotrophic lateral sclerosis (ALS), multiple system atrophy, Huntington's disease…). In most cases, gliosis involves the proliferation or hypertrophy of several different types of glial cells. In its most extreme form, the proliferation associated with gliosis leads to the formation of a glial scar. The ultimate function of the glial scar is to reestablish the physical and chemical integrity of the CNS. [1]

2. Extensive demyelination of white matter caused by intrathecal administration of chemotherapeutic agents (toxic leuoencephalopathy) (Fig. 2 on page 8)

Intrathecal chemotherapy is the introduction of chemotherapy drugs into the cerebrospinal fluid by injection into the subarachnoid space of the spinal cord in order to bypass the blood-brain barrier. Indications can be therapeutic (carcinomatosis meningitis), as well as prophylactic (leukemias/lymphomas with high risk of CNS involvement). Intrathecal chemotherapy drugs can cause toxic leucoencephalopathy with a significant increased risk in those patients receiving concurrent radiotherapy.

The term "toxic leucoencephalopathy" encompasses a wide spectrum of diseases that may injure and cause structural alteration of the white matter; the injuries can be toxic and metabolic secondary to chemotherapy or immunosuppressive therapy, environmental, or infectious in its origin [2].

It is important to distinguish the MRI appearance of acute toxic leucoencephalopathy from another reversible entity, posterior reversible encephalopathy syndrome (PRES)
(Fig. 3 on page 9), which can be caused by many of the same medications or drugs; however, posterior reversible encephalopathy syndrome is thought to involve the cortex and subcortical white matter in mild cases on FLAIR and to extend into the periventricular white matter in severe cases only, with restricted diffusion in a minority of cases [3,4].

3. Posterior reversible encephalopathy syndrome (PRES) induced by chemotherapy (Fig. 3 on page 9)

The posterior reversible encephalopathy syndrome (PRES) also known as reversible posterior leucoencephalopathy syndrome (RPLS), is described clinically as an acute neurological deterioration, characterized by headache, impairment of mental status and seizures. Although the pathophysiological mechanism(s) of this syndrome has not been fully understood, it is thought that PRES results from vasogenic edema in areas of the brain supplied by the posterior arterial circulation. Firstly, this syndrome was recognized in patients with severe hypertension but has now been described in patients with a variety of clinical conditions including preeclampsia/eclampsia, autoimmune disease, infection/sepsis/shock, transplantation, hypertension, cancer chemotherapy etc. [5,6].

In patients on cancer chemotherapy, PRES is usually encountered after high-dose multidrug cancer therapy, typically in hematopoietic malignancies [7]. A variety of cancer chemotherapeutic drugs have also been noted in association with PRES (Cytarabine, Cisplatin, Gemcitabine, Tiazofurin, Bevacizumab (Avastin), etc.).

Magnetic resonance imaging (MRI) studies typically reveal a unique pattern of symmetrical changes in the subcortical white matter of the cerebrum [8].

4. Progressive multifocal leukoencephalopathy (PML) induced by systemic immunosuppressive therapy (Fig. 4 on page 10)

Progressive multifocal leukoencephalopathy (PML) is a fatal opportunistic infection of the central nervous system caused by reactivation of the polyomavirus JC (JCV), typically seen in individuals with profound cellular immunosuppression [9]. There is increased reporting of patients with systemic lupus erythematosus (SLE) developing PML while on intensive immunosuppressive therapy. In spite of the grave prognosis associated with PML, these patients can have an excellent outcome if immunosuppressants are discontinued as soon as the correct diagnosis is made. [10,11,12,13].

5. Parenchymal brain volume loss in children receiving CNS prophylaxis with radiation therapy (Fig. 5 on page 11) or intrathecal chemotherapy
Patients undergoing radiation for primary brain tumors, skull lesions, or intracranial metastasis frequently exhibit central and cortical parenchymal loss. Children receiving CNS prophylaxis with irradiation or intrathecal chemotherapy may eventually develop cerebral volume loss, even when CNS leukemic involvement was not originally present. This finding correlates with posterior neurocognitive deficits, more severe in the youngest group of patients. [14]

When the enlargement does not reverse after remission but instead persists or even increases, it is probably related to cranial irradiation and is responsible for posterior learning problems in up to 80% of survivors [15].

6. Cerebral radiation necrosis (Fig. 6 on page 12)

The radiologist’s challenge in the postradiotherapy evaluation is to differentiate residual or recurrent tumor from radionecrosis. Several factors influence the development of radiation necrosis (total dose, overall time of administration, size of each fraction of irradiation, number of fractions per irradiation, patient age, and survival time of patients). As patients survive longer with more effective treatment, the incidence of radiation necrosis will rise, because it is usually a late effect of treatment. The signs and symptoms of radiation necrosis are nonspecific and do not differentiate it from recurrent tumor. The effects of irradiation have been separated into those occurring early (within weeks) and late (4 months to many years later). The delayed effects are separated into early delayed injury (within months after therapy) or late injury (months to years after therapy). The late effects are usually irreversible, affect white matter to a much greater extent than gray matter, and histologically involve vascular changes that include coagulative necrosis and hyalinization. The late injury to the brain may be focal or diffuse and occurs in approximately 5% to 15% of irradiated patients.

Unfortunately, it is exceedingly difficult to make the diagnosis of focal radiation injury. Some investigators are using Magnetic Resonance Spectroscopy (MRS) and perfusion imaging (PWI) to determine whether necrotic areas after radiotherapy are due to tumor or radiation.

Slight increase in choline/creatine (Cho/Cr) ratio in radiation necrosis may be an important MRS criteria in distinguishing this entity from recurrent high-grade primary neoplastic infiltration, where the aforementioned ratio is significantly increased.

PWI also shows marked role in differentiating radiation necrosis from recurrent tumor on the basis of differences in blood-brain barrier permeability. Furthermore, radiation damage is hypoperfused; most high-grade tumors show increased flow [16,17,18]. Unenhanced arterial spin-labeled (ASL) imaging may more accurately distinguish
predominant recurrent high-grade glioma from radiation necrosis, compared with
dynamic susceptibility contrast-enhanced cerebral blood volume (DSCE-CBV) magnetic
resonance imaging, especially in regions with mixed radiation necrosis. [19]
Fig. 1: MR imaging after surgical resection for left frontal low-grade astrocytoma (grade II). Axial T2W and FLAIR images (A, B) - parenchymal defect of the left frontal lobe and perilesional zone of high-intensity signal, with no significant diffusion restriction (C and D). Axial T1W image after contrast administration (E) shows no area of contrast enhancement, with decreased vascularisation on ASL PI (F). Single-voxel MR spectroscopy with long echo - TE 135ms (G) shows decreased peaks of metabolic compounds (Cho, Cr and NAA) with myoinositol peak, consistent with glial scar.

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Fig. 2: A 46-year-old man receiving intrathecal chemotherapy due to leptomeningeal carcinomatosis, presenting with headaches and generalised seizures. Initial MRI (A1,2): axial T2W (A1) and FLAIR images (A2) show severe high-intensity abnormality of periventricular white matter. Control MRI after 1 month (B1,2) and 3 months (C1,2) show progression of extensive demyelination of white matter caused by intrathecal administration of chemotherapeutic agents (toxic leukoencephalopathy).

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**Fig. 3:** Posterior reversible encephalopathy syndrome (PRES) induced by chemotherapy. A 36-year-old woman with cervix carcinoma received combined radiochemotherapy including cisplatin. Patient suddenly became somnolent, developed a mild paresis of right arm with focal seizures and visual impairment. MRI exam was performed (A1-3): bilateral high-intensity foci abnormality on FLAIR, in the cortex and subcortical white matter of the occipital and frontal region. Control MRI scan after 25 days (B1-3) shows no previously seen high-intensity abnormality, with no clinical symptoms, either.

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Fig. 4: Progressive multifocal leukoencephalopathy (PML) induced by systemic immunosuppressive therapy - a 39-year-old woman with known SLE (diagnosis of SLE was made at the age of 29) presented progressive left-side weakness developing over two weeks. At the time she was taking oral prednisone and mycophenolate. First exam (A1-3): Axial T2W image (A1) and axial FLAIR (A2) shows huge lesion in the right subcortical fronto-parietal region with increased T2W signal, associated with elevated concentration of lactate, shown on MR spectroscopy with long echo - TE 135ms, a product of anaerobic glycolysis, typical for PML (A3). There was no enhancement on gadolinium administration (image not shown). Control exam 7 months later (B1-3) shows regression of PML foci on axial T2W image (B1) and FLAIR (B2), as well as height of lactate peak, and increased concentration of N-acetyl aspartate (B3), a marker of neuronal activity, compared to prior MR study. At the same time, patient shown improvement of left arm weakness.
Fig. 5: A 11-year-old patient with leukemia (but without CNS leukemic involvement) receiving chemotherapy and prophylactic endocranial radiation therapy (A1,2). Axial T2W image (A1) and axial FLAIR (A2) shows widely dilated ventricular and subarachnoid spaces comparing with age-matched control (B1,2) - Cerebral parenchymal volume loss.

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Fig. 6: Radiation necrosis - MR imaging after surgical resection, radiation, and chemotherapy for left occipital glioblastoma multiforme. Axial T2W (A) and FLAIR (B) - parenchymal defect of the left occipital lobe and large zone of edema in the left occipital and temporal lobes. Axial T1W image after contrast administration (B) shows an area of contrast enhancement, with decreased vascularisation on ASL PI (C) and with no significant diffusion restriction (D and E). MR spectroscopy with long echo - TE 135ms (F) shows decreased peaks of Cho, Cr and NAA, with increased peak of lipid, consistent with radiation necrosis.

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Conclusion

Magnetic resonance imaging (MRI) plays a major role in the detection and evaluation of iatrogenic brain parenchyma injury.

MRS and PWI increase the sensitivity and specificity of the differentiation between residual/recurrent neoplastic process and posttreatment changes.
References


