Radiation-Induced Leukoencephalopathy in Glioma Patients

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Abstract

Radiation-induced leukoencephalopathy (RIL) is a late complication of cerebral radiation therapy (CRT) used in treating gliomas. It involves progressive damage to the brain's white matter, seen as T2/FLAIR hyperintensity on MRI. Risk factors include age, high radiation doses, and cumulative exposure. RIL is caused by mitochondrial dysfunction, blood-brain barrier disruption, and oligodendrocyte apoptosis, leading to neurocognitive decline, ranging from mild memory issues to severe dementia. While no cure exists, treatment focuses on managing symptoms, and research is exploring ways to minimize risk through lower radiation doses and targetted therapies. This review aims to summarize key findings on RIL, focusing on its epidemiology, pathogenesis, clinical manifestations, and existing treatments.

Keywords: Radiation-induced leukoencephalopathy, Radiation, Glioma, Degeneration, Oligodendrocyte.

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Introduction

Gliomas are the most common primary intracranial tumour, constituting over 80% of malignant primary brain tumours.[1] Cerebral radiation therapy (CRT), in conjunction with surgery and chemotherapy, to target and destroy malignant cells has been crucial in prolonging survival in patients with high-grade gliomas, especially when complete surgical resection poses a potential challenge. A study indicated that high-grade glioma (HGG) patients receiving concurrent post-surgery chemo-radiotherapy exhibited improved overall survival (OS) and progression-free survival (PFS), with median OS extending up to 25.6 months.[2] However, CRT is neurotoxic, and of all neurological complications precipitated by RT, the most common and serious delayed complication is termed Radiation-Induced Leukoencephalopathy (RIL).[3] In this narrative review, we attempt to review the literature around RIL, focussing on its epidemiology, pathogenesis, clinical manifestations, and existing management options.

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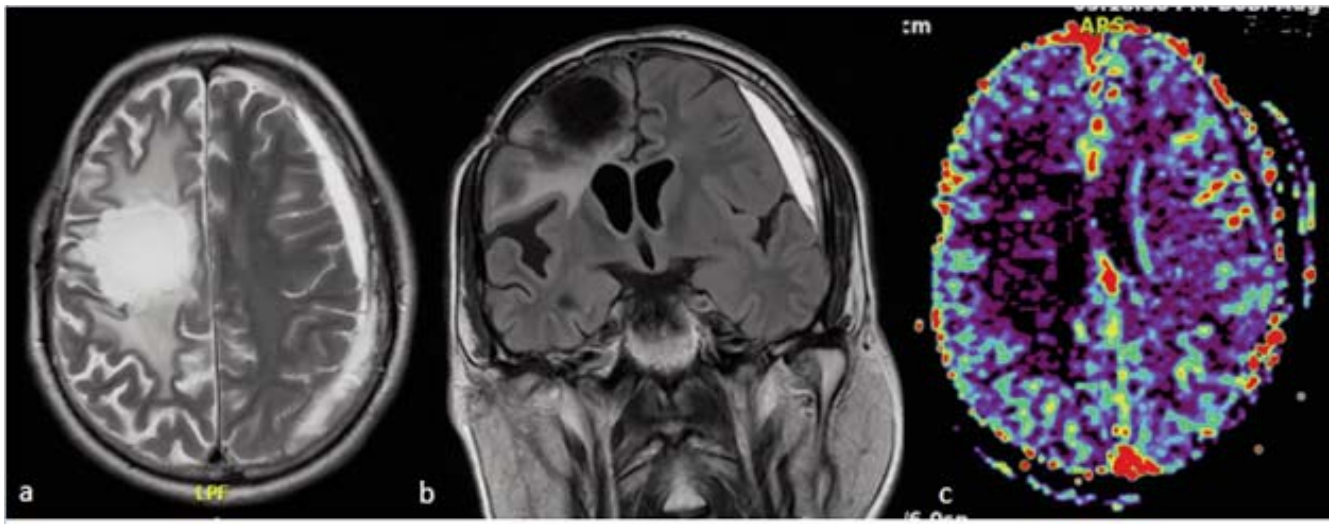
Review of the Literature

RIL is a degenerative disorder of the cerebral white matter orchestrated by necrosis of the white matter secondary to radiologic insult.[4] It is a late-onset complication, as shown by a randomized dose-escalation trial by Corn et al., who found the median time to develop moderate to severe radiographic changes consistent with RIL in their patient sample was 14.5 months.[5] The incidence of RIL in glioma patients is high; a study involving 81 patients with HGG treated with postoperative CRT, 44 (54.3%) developed RIL.[6]

Risk factors for RIL are manifold. Given its degenerative nature, it is shown to vary positively with time post-CRT, as shown by Terziev et al., who found the cumulative incidence of RIL to increase in their HGG cohort over time, from 21% at 12 months to 48% at 60 months.[6] They also found advanced age to be a risk factor for RIL, with 54% of HGG patients aged over 60 developing RIL 12 months post-CRT compared to 15% in those less than 60 years of age.[6] Smoking too was found to be significantly associated with earlier onset of RIL.[6] Calabrese et al. highlighted higher radiation dosages were associated with worse clinical manifestations of RIL, while delayed CRT in low-grade gliomas (LGG) could potentially reduce the risk of RIL without compromising outcomes.[7]

The cellular and pathophysiological mechanisms orchestrating RIL are multifactorial, with the primary precipitant being radiation that induces the production of mitochondrial reactive oxygen species (mtROS) and causes mitochondrial DNA damage in endothelial cells which ultimately increases the blood brain barrier (BBB) permeability and eventually disrupts it.[8,9] This vascular endothelial dysfunction is associated with cognitive decline, consistent with the existing literature reporting that whole-brain irradiation (WBI) results in a decline in neurocognitive function in about 50% of patients.[10] Additionally, oligodendrocytes and their progenitor cells (OPCs), being extremely sensitive to radiation, are directly targetted and resultantly undergo apoptosis and demyelination.[11] A cascade of inflammation following CRT further exacerbates neuronal injury and cognitive



Figure(a,b,c): Arrow pointing at the right lower parathyroid gland in the picture. Stitch is retracting the right lobe of the thyroid gland medially.

impairment and is also implicated in aiding BBB disruption.[12]

Cognitive decline is the primary and most evident manifestation of RIL, with patients suffering from a range of symptoms including learning difficulties and memory loss.[13] RIL as a disease entity includes levels of severity ranging from mild to severe, with the most severe patients progressing to developing overt dementia.[6,13] The rate of cognitive decline has been found to vary with age, with older patients tending to undergo more rapid decline compared to younger patients in whom cognitive faculties often remain better preserved until very advanced age.[14] RIL's degenerative pathogenesis concentrated on the cerebral white matter tracts can be discerned from its radiologic picture involving T2/FLAIR hyperintensity in the cerebral white matter, along with ventriculomegaly and cerebral atrophy.[13] (Fig 1 a,b,c) These changes seem to be more apparent in brain regions concerned with higher mental functions and complex cognitive processes such as the hippocampus and frontal lobe of the brain.[3,13]

RIL has the potential to significantly impair the quality of life of patients who have already undergone much tribulation to mitigate the threat of a brain tumour. Like most neurodegenerative pathologies, however, there exists no cure for it, with available treatments aimed only at providing symptomatic relief.[3] Efforts must therefore be concentrated on implementing preventive strategies.[3] There is evidence in the literature to suggest that reducing radiation doses and using stereotactic radiation techniques rather than whole-brain radiation may be associated with a reduced risk of RIL, though more research is needed to elucidate the actual strength of these associations, for there is the possibility of confounding as cognitive decline can be associated with recurrence or worsening of the primary disease process much as with the neurotoxic treatment received for it.[7,15] More human studies aimed at investigating these relationships more closely will be of benefit in this regard.

Conclusion

RIL is a debilitating late complication of CRT with the potential to orchestrate devastating cognitive decline. Both patient and treatment-centric factors contribute to producing the observed severity of the disease in individual cases. There still exists no treatment to reverse the degenerative changes in the brain though symptomatic alleviation is possible and practiced. More research is needed to elucidate the relationship between the dose of radiation delivered and the volume of brain irradiated with it and the risk of developing RIL to make the development of better preventive strategies possible.

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