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Pathological review of late cerebral radionecrosis

Abstract Late cerebral radionecrosis may be considered to be a specific chronic inflammatory response, although it is unknown whether the initial damage by brain irradiation is to an endothelial cell or a glial cell. I discuss the pathological specificity of late cerebral radionecrosis by studying the published literature and a case that I experienced. In late cerebral radionecrosis, there are typical coagulation necrosis areas containing fibrinoid necrosis with occlusion of the lumina and poorly active inflammatory areas with many inflammatory ghost cells, focal perivascular lymphocytes, hyalinized vessels, and telangiectatic vascularization near and in the necrotic tissue, and more active inflammatory areas formed as a partial rim of the reactive zone by perivascular lymphocytes, much vascularization, and GFAP-positive astrocytes at the corticomedullary border adjacent to necrotic tissue in the white matter. It is difficult to believe that coagulation necrosis occurs without first disordering the vascular endothelial cells because fibrinoid necrosis is a main feature and a diffusely multiple lesion in late cerebral radionecrosis. Because various histological findings do develop, progress, and extend sporadically at different areas and times in the irradiated field of the brain for a long time after radiation, uncontrolled chronic inflammation containing various cytokine secretions may also play a key role in progression of this radionecrosis. Evaluation of the mechanism of the development/aggravation of late cerebral radionecrosis requires a further study for abnormal cytokine secretions and aberrant inflammatory reactions.

Key words Late cerebral radionecrosis · Endothelial cell damage · Inflammatory response · Cytokine · Progression

Introduction

Late cerebral radionecrosis is observed at radiotherapy doses less than 50 Gy but generally increases with increasing radiation dose, fraction size, and the administration of chemotherapy.

Classically, hypotheses of initial vascular damage or initial glial damage have been proposed as the cause of late cerebral radionecrosis. For the vascular damage hypothesis, radiation-induced endothelium damage may lead to microvascularopathy, resulting in vascular insufficiency and infarction followed by gray and/or white matter necrosis. The blood–brain barrier (BBB) becomes disrupted by the vulnerability of the endothelial cells to radiation and interactions between those endothelial cells and the inflammatory cells that migrate as a result of the radiation-induced inflammatory response. Many of those vessels show perivascular infiltration of T lymphocytes and macrophages.

Milliat et al. reported that secretion of transforming growth factor-beta (TGF-β) 1 was increased after irradiation of endothelial cells and that endothelial cells influenced the fundamental mechanisms involved in radiation-induced vascular damage. Gaugler et al. reported in vivo evidence of a bystander effect, secondary to endothelial cell damage, in tissue response to radiation.

On the other hand for the glial damage hypothesis, radiation-induced glial damage may lead to ablation of glial precursors and result in demyelinating necrosis. Chow et al. reported that ionizing radiation-induced apoptosis occurred in oligodendrocytes that were postmitotic cells in the adult mouse central nervous system (CNS) and that this process was p53 dependent. In radionecrosis, interleukin-1 alpha, tumor necrosis factor-alpha, and interleukin-6 are expressed, predominately by infiltrating macrophages. DeLegge et al. suggested a link between the inflammatory response, increased cytokine formation, and neurodegen-