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Pathologic Features of Brain Hemorrhage After Radiation Treatment: Case Series with Somatic Mutation Analysis

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Highlights

- Hemorrhagic AREs display primordial cavernous-like changes and telangiectasias
- Hemorrhagic AREs have been called cavernous-like malformations or pseudocavernomas
- Gene sequencing shows variants in *PIK3CA* and *PTEN* but not in *CCM* genes
- Mutations converge on pathways implicated in endothelial dysfunction

ABSTRACT

Background

Radiation treatment for diseases of the brain can result in hemorrhagic adverse radiation effects. The underlying pathologic substrate of brain bleeding after irradiation has not been elucidated, nor potential associations with induced somatic mutations.

Methods

We retrospectively reviewed our department's pathology database over 5 years and identified 5 biopsy specimens (4 patients) for hemorrhagic lesions after brain irradiation. Tissues with active malignancy were

excluded. Samples were characterized using H&E, Perl's Prussian Blue, and Masson's Trichrome; immunostaining for B-cells (anti-CD20), T-cells (anti-CD3), endothelium (anti-CD31), macrophages (anti-CD163), α-smooth muscle actin, and TUNEL. DNA analysis was done by two panels of next-generation sequencing for somatic mutations associated with known cerebrovascular anomalies.

Results

One lesion involved hemorrhagic expansion among multifocal microbleeds that had developed after craniospinal irradiation for distant medulloblastoma treatment. Three bleeds arose in the bed of focally irradiated arteriovenous malformations (AVM) after confirmed obliteration. A fifth specimen involved the radiation field distinct from an irradiated AVM bed. From these, 2 patterns of hemorrhagic vascular pathology were identified: encapsulated hematomas and cavernous-like malformations. All lesions included telangiectasias with dysmorphic endothelium, consistent with primordial cavernous malformations with an associated inflammatory response. DNA analysis demonstrated genetic variants in *PIK3CA* and/or *PTEN* genes but excluded mutations in *CCM* genes.

Conclusions

Despite pathologic heterogeneity, brain bleeding after irradiation is uniformly associated with primordial cavernous-like telangiectasias and disruption of genes implicated in dysangiogenesis but not genes implicated as causative of cerebral cavernous malformations. This may implicate a novel signaling axis as an area for future study.

Section snippets

INTRODUCTION

Benefits of radiation treatment are severely limited by adverse radiation effects (ARE), also referred to as radionecrosis, with a reported incidence of 5-68% after brain irradiation[1]. Clinical and imaging definitions have not been consistent[2], and the specific prevalence of brain bleeding within the context of ARE is not known. Pathologic substrates and molecular features of hemorrhagic ARE have not been systematically studied[3].

Herein we report a series of 5 ARE lesions with confirmed brain…

METHODS

Our department's neurovascular pathology database was queried from 2018-2022 and identified 4 patients who underwent 5 biopsies for ARE, and had manifested evidence of hemorrhage on brain MRI (Figure 1). Tissues with active malignancy were excluded. Search criteria and methods for histology, immune-multiplexing, immunohistochemistry, DNA sequencing and mutation analyses are detailed in the Supplementary Methods. All patients had provided written consent for tissue collection in accordance with…

Histopathologic Characterization

One lesion developed among multifocal microbleeds outside the tumor bed after craniospinal irradiation for medulloblastoma treatment. Three cases arose in the bed of focally irradiated arteriovenous malformations (AVM) after confirmed obliteration. A fifth specimen was isolated from a site distinct from an irradiated AVM bed. The clinical presentations and histological findings are detailed in the Supplementary Results (Tables S1

and S2). We identified encapsulated hematomas and cerebral…

DISCUSSION

It has been shown that radiation triggers endothelial injury with fibrin deposition in blood vessels, leading to progressive luminal occlusion and wall thickening in association with immune cell infiltration[6]. This likely results in ischemia and infarction[3], and a hypoxia response mechanism that initiates neovascularization, with VEGF implicated as a substrate[1,3].

Previous reports have described post-radiation microbleeds, CCMs, pseudocavernomas, cystic hemorrhagic radiation necrosis, and…

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CRediT authorship contribution statement

Roberto J Alcazar-Felix: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing, Validation. **Abhinav Srinath:** Conceptualization, Methodology, Supervision, Writing – original draft, Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – review & editing. **Stephanie Hage:** Conceptualization, Formal…

Declaration of competing interest

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None…

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