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Letters to the Editor

Cognitive function, cerebral microbleeds, radiotherapy, and bevacizumab in survivors of pediatric brain tumors

We read with great interest a recent paper published by Roddy et al showing a high (48.8%) 5-year cumulative incidence of cerebral microbleeds (CMB) and its association with cognitive dysfunction in a group with pediatric brain tumors who received cranial radiation therapy (CRT).[1] We believe that exposing the association of CMB (or the associated underlying microvascular pathology) with cognitive impairment in this population will help draw attention to the importance of the topic in this specific growing population. In a retrospective cohort study from our institution with 132 pediatric brain tumor patients designed to address the correlation between CRT focus/dosage with the topographic location of CMB using the Microbleed Anatomical Rating Scale, we also found CMB in a high percentage (41.5%) of patients (unpublished manuscript, Passos et al). It is worthwhile to highlight that operational CMB definition, assessment methodology, and follow-up duration all affect CMB prevalence.[2] In the study by Roddy et al, a small number of patients (n = 7) treated with bevacizumab had an increased incidence of CMB. Bevacizumab was most probably used in specific tumors (high-grade gliomas) or circumstances (medulloblastoma recurrence) which could be per se more prone to CMB after CRT.[3,4]The dynamic nature of radiation-induced microvasculopathy must also be taken into account. We have already shown that these lesions can progress from CMB to cavernomas (Fig. 1, illustrative case), and there are anecdotal cases of incidental regression of CRT-induced cavernomas after bevacizumab treatment.[5] It would be of interest to replicate these findings and to compare the frequency of CMB and cavernomas in post-CRT survivors of pediatric brain tumors treated and not treated with bevacizumab. Disentangling this puzzle can possibly help to find strategies to modify the natural history of chronic microvascular complications after CRT.

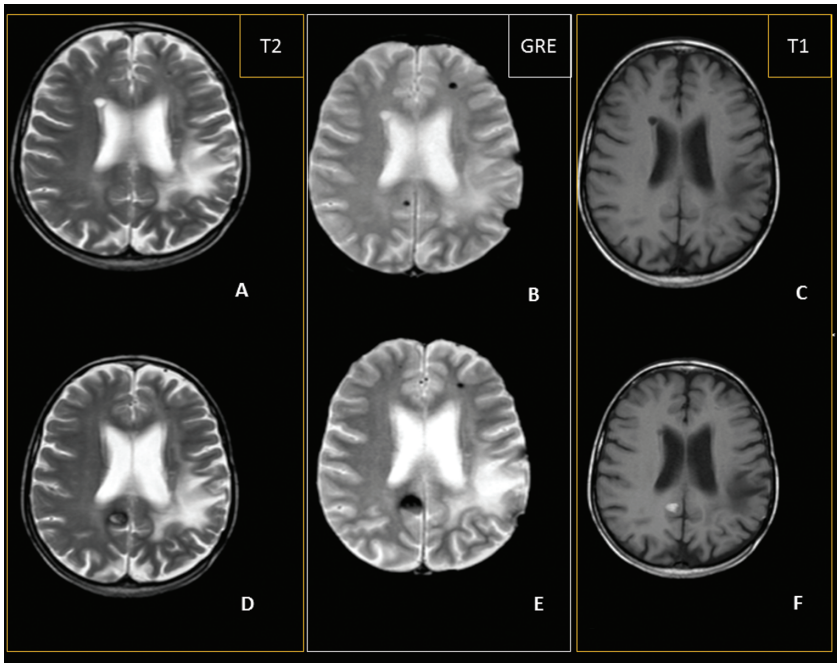

Fig. 1 Follow-up brain MRI with gradient recalled echo (GRE)/ T2* sequence of a 27-year-old survivor of childhood primary brain tumor, showing evolution of a radiation-induced microbleed (1A–C) to a cavernoma (1D–F) in 20 months. Classification according to the current definitions.[6,7]

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Response to "Cognitive function, cerebral microbleeds, radiotherapy, and bevacizumab in survivors of paediatric brain tumors"

We thank the authors for their reply to our article. We agree that it is of utmost importance to disentangle the complex determinants of microvasculopathy development as well as the determinants of potential regression in this vulnerable population of pediatric brain tumor patients. We find that their demonstration that radiation-induced cerebral microbleeds (CMBs) can progress to cavernomas to be an important observation. Although this was not a specific end point of our study, we did note that one patient in our cohort had a CMB that developed into a cavernous malformation. We have previously reported that cavernous malformations are common in survivors of pediatric brain tumors who received radiation and can present on a spectrum of histological features.[1] It is our goal to continue to follow this cohort of patients to observe the natural history of these lesions.

Regarding the use of bevacizumab, we acknowledge that the population who received this drug may have been unique. However, there was no significant difference in tumor type or rate of tumor recurrence between patients who developed CMBs and those who did not (Table 1).[2] Post-hoc analysis of patients who received bevacizumab demonstrates that the rate of recurrence between patients who received bevacizumab and those who did not was not statistically different (36% and 20%, $P = .145$), though patients with high- or low-grade gliomas were more likely to receive bevacizumab (67% versus less than 10% for all other tumor types, $P = .004$). Interestingly, others have shown that administration of the anti-angiogenic drug enzastaurin with cranial radiation therapy was associated with decreased rate of additional CMB formation in adults. The underlying etiology for this was hypothesized to be a potential radioprotective effect of the anti-angiogenic therapy on microvasculature by decreasing capillary permeability and cytokine release.[3]

Determining the role specifically of bevacizumab on CMB development was not the focus of our study, and given that we had only 14 patients who received bevacizumab, more numbers are needed to further study the effect of bevacizumab on CMB development and potential evolution.

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