A case of co-occurrence of radiation-induced leukoencephalopathy and CADASIL

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CASE

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PRACTICAL IMPLICATIONS

Consider an underlying genetic cause in patients with progressive deterioration and leukoencephalopathy after prophylactic radiotherapy.

We present a 63-year-old woman who was diagnosed with a stage IIIA malignant neuroendocrine tumor of the lung at 57 years of age. Her medical history was otherwise unremarkable besides a history of smoking. She was treated with chemoradiotherapy (cisplatin/etoposide, 67.5 Gy) and underwent prophylactic cranial irradiation (PCI; 25 Gy in 10 fractions). Prior to PCI, MR imaging of the brain showed an old right parietotemporal lacunar infarct and mild periventricular white matter hyperintensities (WMHs) (figure, A and B). Two years later, at age 59 years, she started to suffer from subacute paroxysmal neurologic deficits consisting of aphasia, dysarthria, paresis of one or both legs and bradyphrenia, sometimes accompanied by unilateral headache. ECG and carotid duplex were normal. MR imaging showed profound progression of periventricular WMH to subcortical areas with sparing of the subcortical U fibers (figure, C and D). Enlargement of perivascular spaces was present in the basal ganglia. On suspicion of a vascular origin, she was put on antiplatelet therapy, but the attacks persisted the following years. The duration varied between several minutes to hours, and eventually one attack lasted several weeks. After each attack, the neurologic deficits largely resolved, although cognitive functioning gradually deteriorated and her gait increasingly worsened with marked start hesitation and postural instability. During one of these attacks, EEG revealed profound asymmetric slowing of cerebral activity but without epileptic discharges. Lumbar puncture excluded an infectious or paraneoplastic origin, and recurrence of the NET was excluded by CT-PET imaging (both fluorodeoxyglucose and Gallium-68 Edotreotide). MR imaging of the brain showed further progression of WMH (figure, E and F) and profound cortical and subcortical atrophy developed, suggestive of radiation-induced leukoencephalopathy (RIL). Her neurologic attacks were considered as transient ischemic attacks, complex partial seizures or strokelike migraine attacks after radio therapy (SMART) syndrome, but no unequivocal diagnosis could be established. Because of the unexpectedly extensive WMH after low radiation doses, additional genetic testing was performed. Next-generation sequencing of 26 genes involved in adult-onset leukoencephalopathy (available upon request) identified a pathogenic missense mutation in exon 14 of the *NOTCH3* gene (c.2182C > T p.(Arg728Cys)), which is consistent with the genetic diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Family history was negative for neurologic diseases.

Discussion

This case report illustrates that patients with RIL may have an underlying (unrecognized) hereditary small-vessel disease. RIL is one of the late adverse effects of brain radiation, and it is not well understood why some patients are more sensitive than others to develop late side effects. Older age (>65 years), dose per fraction, total dose, and the presence of white matter lesions prior to radiotherapy are risk factor for the development RIL.[1,2] An incidence rate of 14% was reported in patients treated with PCI,[3] and 34% in patients treated with whole-brain radiation therapy for brain metastases.[4] Our observation of a combination of CADASIL and

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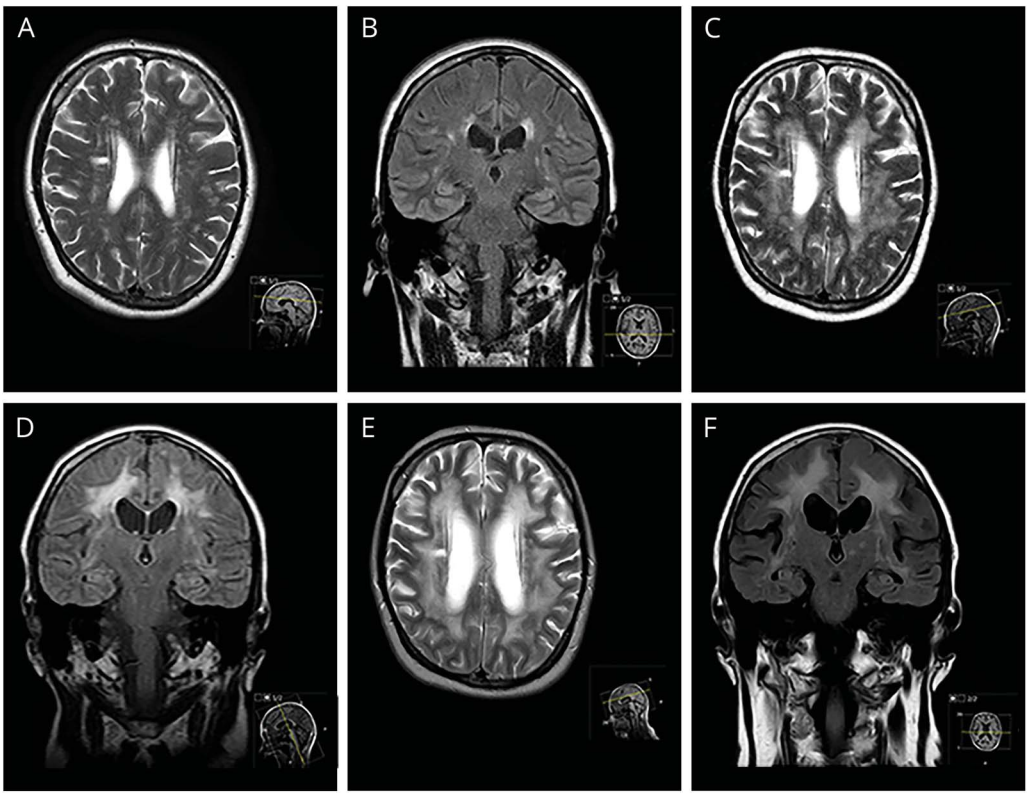
Figure MRI



T2-weighted (A, C, and E) and FLAIR (B, D, and F) MR images at 57 years (A and B) prior to brain radiation, at 59 years (C and D) at symptom onset, and at 63 years (E and F).

RIL in the same patient triggers the question whether a genetic predisposition for hereditary small-vessel diseases is more frequent in patients with RIL or increases the risk of RIL. Detrimental effects of chemotherapy and smoking may have also contributed to the deterioration in our case.

It is difficult to radiologically discriminate between extensive RIL and advanced CADASIL. Moreover, clinical symptoms between the 2 diseases overlap: CADASIL is typically characterized by a history of migraine with aura, followed by recurrent strokes leading to gait difficulties, urinary problems, pseudobulbar palsy, and progressive cognitive decline. Symptoms in patients with RIL include gait problems, urinary incontinence and cognitive decline which develop several months to (many) years after radiation. Our patient suffered from gait disturbances, cognitive decline, and recurrent neurologic deficits. The exact nature of these attacks are difficult to determine. SMART syndrome typically occurs in young adults who are treated with a high radiation dose (more than 50 Gy) for cerebral malignancies, and brain imaging in the acute phase shows unilateral cortical edema and swelling, eventually with enhancement and cortical laminar necrosis,[5] which was not present in our patient. In CADASIL, an acute self-limiting encephalopathic illness has been described, designated as "CADASIL-coma," with headache, fever, confusion, coma, and fits.[6] No fever or seizures were present in our case. Interestingly, family history was unremarkable and did not point toward CADASIL, although the father died suddenly at age 60 of an unknown cause. The present *NOTCH3* mutation is a cysteine-altering amino acid change and located in epidermal growth factor-like repeat (EGFr) domain 18. *NOTCH3* mutations outside of EGFr domains 1–6 can be associated with a milder phenotype, presenting at later age and with longer survival, and are frequent in the general population.[7] We can only speculate on symptom onset in our case if no PCI would have been applied.

We conclude that a combination of both CADASIL and RIL is responsible for the clinical symptoms. Future genetic studies in patients with RIL after prophylactic irradiation may help to explore this association.

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Mark C. Kruit, MD, PhD	Department of Radiology, Leiden University Medical Center	Interpreted the data and revised the manuscript
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Frank Baas, MD, PhD	Department of Clinical Genetics, Leiden University Medical Center	Performed the genetic studies; interpreted the data and revised the manuscript
Saskia A.M.J. Lesnik Oberstein, MD, PhD	Department of Clinical Genetics, Leiden University Medical Center	Interpreted the data and revised the manuscript

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