Intracerebral pseudotumors in a family with cerebroretinal vasculopathy

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A 33-year-old Hispanic woman presented to our facility with headache, blurry vision, worsening right hemiparesis, and new left hemiparesis. Her past medical history was significant for previous admission to an outside facility at age 31 for acute onset of right hemiparesis attributed to leukoencephalopathy with cysts. Family history revealed that the patient's mother, 2 maternal uncles, and maternal grandfather had surgical resection of "brain tumors." The latter 2 also developed blindness. Neuroimaging revealed extensive right cerebral vasogenic edema with an associated 8×9 mm heterogeneously enhancing right frontal lesion, left subfalcine herniation, and additional heterogeneous lesions in both cerebral hemispheres (figure 1). CSF analysis revealed 1 leukocyte/mm³, glucose of 42 mg/dL, protein of 145 mg/dL, increased immunoglobulin G (IgG) production with an IgG index of 0.81, and no oligoclonal bands. An extensive serum, CSF, infectious, and rheumatologic workup was otherwise negative. Neuroimaging following a stereotactic biopsy revealed worsening right cerebral vasogenic edema with increased midline shift prompting initiation of low dose oral dexamethasone without clinical improvement. Stereotactic and subsequent open brain biopsy revealed a necrotizing process predominantly involving the subcortical white matter with sparing of the cortex and large areas of infarct-like necrosis associated with thickened and hyalinized small blood vessels, which closely resembled changes seen with radiation-induced leukoencephalopathy (figure 2). There was no clinical history of prior irradiation. There was no evidence of an underlying neoplasm, vasculitis, inflammatory process, or infection. Retinal examination revealed arterial sheathing with associated large cotton-wool spots, and dot-blot hemorrhages in the periphery.

Further review of the medical record showed that the patient's mother presented to our institution in 2001 with right hemiparesis at the age of 46 and was discovered to have a 2.5-cm enhancing mass in the left parietal lobe with 2 smaller masses in the left frontal and cerebellar regions. Treatment with IV dexamethasone resulted in improved right hemiparesis. A left frontal lesion biopsy led to a diagnosis of metastatic carcinoma of unknown primary. The mother was lost to follow-up and died within 2 years of initial presentation. Review of the mother's biopsy showed similar features to those of the daughter's without evidence of

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Figure 1 Neuroradiologic features of cerebroretinal vasculopathy

(A) T1-weighted contrast-enhanced and (B) T2 fluid-attenuated inversion recovery (FLAIR)-weighted MRI demonstrate a heterogeneous enhancing mass-like lesion in the right frontal lobe with extensive edema and mass-effect causing effacement of the right lateral ventricle and midline shift. Post-steroid treatment (C) T1-weighted contrast-enhanced and (D) T2 FLAIR-weighted MRI demonstrate marked decrease in edema with re-expansion of the right lateral ventricle and resolution of midline shift. MRI of the patient's mother's brain (E) T1-weighted contrast-enhanced and (F) T2 FLAIR-weighted MRI demonstrate heterogeneous mass-like lesions in the left frontal lobe with edema and mass effect similar to the patient's.

carcinoma. The original diagnosis was felt to be a misinterpretation based on nonspecific immunohistochemical findings.

The pathologic review of tissue specimens obtained from both our patient and her mother were suggestive of cerebroretinal vasculopathy, prompting genetic testing that confirmed a mutation of the *TREX1* gene. Our patient was treated with methylprednisolone 70 mg IV daily for 5 days with near-complete resolution of her acute left-sided hemiparesis, lower left facial weakness, dysarthria, and decreased right hemispheric peri-lesional edema. Her chronic right hemiparesis was unchanged. She was continued on an oral prednisone taper and discharged on 20 mg daily. A repeat retinal examination showed resolution of the cotton-wool spots and peripheral hemorrhages. At 4-month follow-up there were no clinical or radiographic changes.

Figure 2 Neuropathologic features of cerebroretinal vasculopathy

Hematoxylin-eosin-stained histologic sections of the brain biopsy (100× magnification) show areas of necrosis with adjacent abnormal vessels (A). At 400× magnification, these vessels show both abundant hyalinization (B) and fibrinoid necrosis (C). These findings strongly resemble changes seen following radiation; however, the patient did not receive radiation.

DISCUSSION

CRV, an autosomal dominant disorder characterized by retinal microvascular abnormalities and tumor-like mass lesions in the subcortical white matter, is caused by mutations in *TREX1*, a gene encoding a 3'-5' DNA exonuclease.¹⁻³ CRV may present with headaches, progressive visual loss, seizures, cognitive decline, and spastic hemiparesis. Our family pedigree demonstrates an autosomal dominant pattern of inheritance with onset in the 4th or 5th decade of life. In the original CRV pedigrees, the ophthalmologic disease generally preceded the CNS disease.^{4,5} In contrast, headaches and hemiparesis with fronto-parietal mass lesions were the initial findings in both our patient and her mother.

Our patient's hemizygous nonsense mutation changed a CAG encoding lysine to a stop codon in the C-terminus of the *TREX1* gene at p.K277X resulting in a truncated protein. The definitive in-vivo function of *TREX1* is unclear,⁶ but mutations alter the distribution of *TREX1* from its wild-type perinuclear localization to a disseminated cytoplasmic localization.⁷ This may trigger a viral-like immune response, resulting in vascular damage. Given the remarkable similarity of the pathology to that of radiation-induced leukoencephalopathy, a high index of suspicion for CRV is warranted in non-irradiated patients developing necrotizing cerebral pseudotumors with histopathology resembling radiation damage.

While our patient's chronic symptoms and underlying lesion remained unchanged, her acute symptoms responded to high dose steroids and symptomatic pulse steroid therapy may be considered in CRV, an otherwise fatal disorder with limited treatment options. Additionally, CRV's autosomal dominant pattern of inheritance warrants genetic testing and counseling in family members, taking into account the medical ethical considerations for genetic disorders with limited therapeutic options.

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DISCLOSURES

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/cp for full disclosures.