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Case report

A 55-year-old female with leukoencephalopathy with cerebral calcifications and cysts: Case report and radiopathologic description

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ABSTRACT

Adult-onset leukoencephalopathies with increased cerebral volume can present a potentially challenging diagnosis for the pathologist. We present the case of a patient with a rare adult-onset disease called *Leukoencephalopathy with cerebral Calcifications and Cysts* (LCC). A 55-year-old woman with a history of morning headaches, mild memory loss, diabetes, and hypertension presented to the emergency department with acute onset altered mental status. CT scan revealed multiple small hypodense lesions in the white matter with calcifications in the bilateral cerebral hemispheres, basal ganglia, pons, and cerebellar hemispheres. MRI showed multiple complex/hemorrhagic cystic lesions with partial enhancement in addition to calcifications bilaterally in the frontotemporal white matter, pons, and cerebellar hemispheres, and diffuse white matter signal abnormality. The differential diagnosis included chronic infection, chronic thromboembolic disease, and neoplasm. The biopsy revealed extensive geode-like mineralization as well as smaller calcifications (calcospherites) with associated sclerosis, Rosenthal fibers, angiomatous proliferation of blood vessels with thrombosis and microbleeds. We discuss the differential diagnosis, radiologic and detailed histologic features of LCC.

1. Introduction

Described by Labrune et al. in 1996, Leukoencephalopathy with Cerebral Calcifications and Cysts (LCC) is a rare leukoencephalopathy reported first in the pediatric population [1]. It was first characterized by the radiologic triad of multiple cysts, calcifications, and diffuse white matter signal abnormality. It was not until 2006 when the first adult case was reported in a 44-year-old woman [2], and in 2009 Kleinschmidt-Demasters et al. described the histologic features of two additional adult cases [3]. The disease most likely represents a ribosomopathy with a recently identified mutation in *SNORD118* [4,5]. Our patient is a 55-year-old female with a prolonged disease course and remarkable radiologic findings. In our discussion we describe in detail the histologic features of LCC and discuss the differential diagnosis that should be included when considering this diagnosis.

2. Report of a case

A 55-year-old Caucasian female with a past medical history of hypertension, diabetes, hyperlipidemia and a six month history of worsening morning headaches and forgetfulness presented to the emergency department with acute onset confusion and left-sided weakness. Physical and neurologic exam was unremarkable. Fundoscopic examination showed no abnormalities. Initial diagnostic workup was notable only for hypoalbuminemia and hyperglycemia. A computer tomography scan of the head showed multiple cerebral and cerebellar cysts in addition to calcifications in the cerebral hemispheres, basal ganglia, pons and cerebellum (Fig. 1a). Cranial magnetic resonance imaging (MRI) showed diffuse white matter signal abnormality on the fluid-attenuated inversion recovery (FLAIR) images, and postcontrast partial cyst enhancement (Fig. 1b–d). CSF was unremarkable and cultures were negative.

An initial stereotactic biopsy revealed only mild gliosis and was not diagnostic. To further characterize the lesion, a craniotomy with excision measuring $2.0 \times 1.9 \times 0.8$ cm was performed. Histologic examination revealed a heterogeneous morphology. The most striking morphologic feature was the presence of extensive

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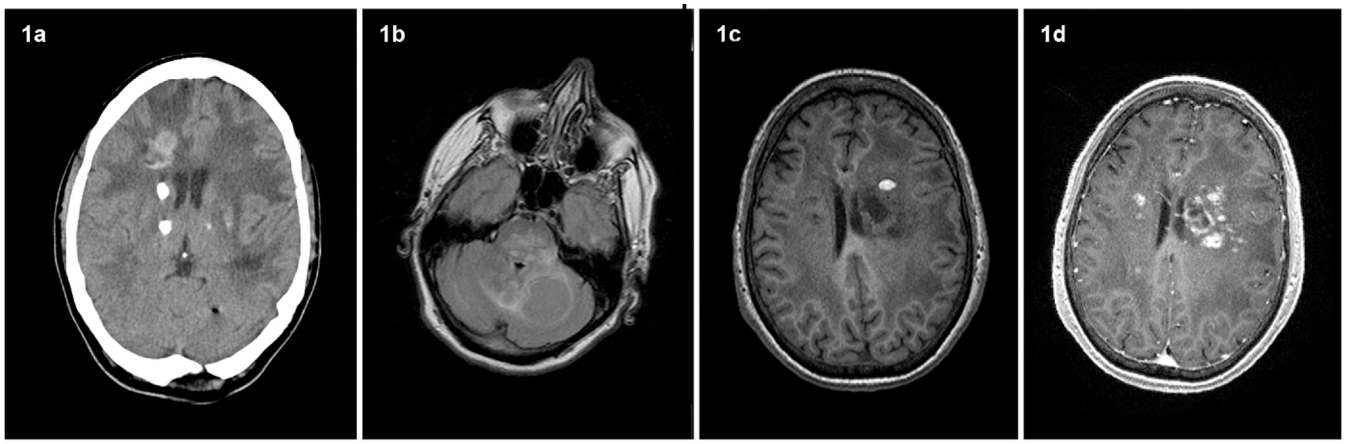

Fig. 1. Axial non-contrast CT image demonstrating bilateral basal ganglionic and thalamic calcification, a partially hemorrhagic cystic lesion in the right frontal lobe, and diffuse bihemispheric leukomalacia (1a). Axial FLAIR MR image demonstrating a left cerebellar complicated cyst as well as cerebellar and pontine edema/gliosis (1b). Axial pre-contrast T1-weighted MR image demonstrating the hyper intense focus of subacute hemorrhage in the left frontal region as well as bihemispheric hypointense areas of cysts and edema (1c). Axial post-contrast T1-weighted MR image demonstrating bihemispheric solid and left hemispheric rim-enhancing cystic lesions (1d).

mineralization, which was seen in two patterns. The most extensive pattern was lamellated, geode-like mineralization (Fig. 2a), which has been described in various chronic neurologic disorders [6]. The second pattern was smaller calcifications consistent with calcospherites at the periphery of the extensive calcifications in a perivascular pattern (Fig. 2b). The adjacent brain parenchyma demonstrated mild, isomorphic fibrillary gliosis with prominent Rosenthal fibers and eosinophilic globules (Fig. 2c). Other areas showed angiomatous changes with thin-walled, small-sized vessels with fibrin thrombi, focal ischemic-type necrosis, micro-bleeds, and associated dystrophic calcifications in the surrounding parenchyma (Fig. 2d). No cytologic atypia or mitoses were seen, and there was no evidence of a cyst lining or remote neurocysticercosis. GFAP immunostain showed mild gliosis with no radiating astrocytes, and CD31 highlighted a decreasing gradient of blood vessels towards the center of the lamellated calcifications (Fig. 3a). To exclude the unlikely possibility of a low-grade neoplasm or infection, immunohistochemical stains revealed the lesion was negative for IDH-1 (R132H) and p53. The MIB-1 proliferative index showed no labeling. PAS showed no staining of deposits within the vessel walls, and Gömöri methenamine silver (GMS) and FITES stains demonstrated no microorganisms.

Table 1
Radiologic and histologic features of LCC.

Radiologic features
• Multiple irregular parenchymal cysts • Calcifications • Diffuse white matter T2-weighted signal abnormality
Histologic features
• Gliosis • Dystrophic calcifications • Angiomatous vessel proliferation with fibrin thrombi and micro-bleeds • Rosenthal fibers and eosinophilic globules

3. Discussion

LCC is a very rare leukoencephalopathy with only 24 adult-onset cases reported, 14 of them including a histologic description. The clinical presentation is variable, ranging from acute neurologic symptoms mimicking a thromboembolic event to a chronic process with mass effect. The hallmark radiologic findings of LCC are multiple, irregular parenchymal cysts, progressive calcifications, and diffuse white matter T2-weighted signal abnormality. The reported histologic features favoring the diagnosis of LCC include gliosis, dystrophic calcifications, angiomatous proliferation of blood vessels with fibrin thrombi, micro-bleeds, and the presence of Rosenthal fibers and eosinophilic globules (Table 1). Recognition of the key histologic features in surgical specimens, the heterogeneous morphology of the disease, and correlation with radiology are essential to avoid unnecessary repeat biopsies. Although distinct in this case, the extensive mineralization cannot be considered diagnostic; however, in our case the feature appears to be unique and consistent with the radiologic impression of extensive calcifications.

Most LCC cases are sporadic, although one case series describes a similar leukoencephalopathy with an autosomal dominant inheritance pattern and reduced penetrance [7]. The most recent studies suggest that LCC is a ribosomopathy characterized by the presence of biallelic mutations in *SNORD118*, which encodes the box C/D small nucleolar RNA (snoRNA) U8 [4,5]. Patient-derived fibroblasts in these patients, in comparison to controls, demonstrate impaired proliferation and a higher percentage of senescent cells; however, there was no association with increased apoptotic activity or disturbances in cell cycling [4]. Our patient was not tested for *SNORD118*, given the mutation was not identified at the time, and the diagnosis was rendered on the constellation of clinical, radiologic and pathologic findings. Nevertheless, identifying the mutation may be necessary in future cases to avoid additional procedures.

Although the pathogenesis of LCC remains unclear, our case suggests an intimate association between the lamellated calcifications and the blood vessels. Our case showed a very striking lamellated, geode-like mineralization with a decreasing concentration of vessels towards the center of the lesions (Fig. 3a). At the periphery of the calcifications, vessels show perivascular calcospherite deposition (Fig. 3b), increasing in density towards the center of the lesions with calcification of the media, expansile lamellation (Fig. 3c), with terminal obliteration of the vessels and coalescence of the calcifications (Fig. 3d). The degree of calcifications with mild gliosis and Rosenthal fibers without reactive or gemistocytic astrocytes is indicative of a longstanding process, in contrast with anisomorphic gliosis which typically shows a haphazard deposition of astrocytic process and occurring in relation to destructive processes. The morphologic features and recent genetic insights suggest that LCC is a degenerating process of blood vessels as a result of dysfunctional