

Case Report

Encephalomalacic dysplastic mass lesion associated with vascular abnormalities in an elderly man. Is this “acquired” focal cortical dysplasia?

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Abstract: Focal cortical dysplasia (FCD) is known to occur in association with a principal lesion and has been newly introduced as FCD type III in the ILAE 2011 classification system of FCDs. FCD type IIIc is associated with vascular malformations, and in all such cases in the literature with histologic confirmation, the principal lesion was a cavernous angioma. We present here a case of mass-forming FCD type IIIc with very unusual vasculopathies. The patient, a 75-year-old man, presented with a seizure and left-sided weakness. MRI showed a right frontal intra-axial mass (4 cm in diameter). He had significant multiple cardiovascular risk factors and a history of melanoma and bladder cancer. Craniotomy was performed for excision of the suspected neoplasm. Histologically, the cortex showed transition from normal, laminar cortical architecture to marked architectural abnormality with irregular areas of encephalomalacia, with intervening, almost nodular regions of “preserved” cortex. These regions consisted of large clusters of dysplastic and maloriented neurons. There were medium-sized to larger arteries with marked medial thickening and luminal stenosis, predominantly within the markedly thickened and fibrosed leptomeninges. In addition, the parenchymal vessels showed markedly hyalinized and thickened walls, and several exhibited glomeruloid clusters of new capillaries. We interpreted the cortical and subcortical encephalomalacic features to be presumably “secondary” to the underlying/associated vascular pathology. This case may represent “acquired” FCD. It is possible that this patient had a preexistent cortical dysplasia with secondary ischemic changes; however, given the absence of previous history of seizure, this appears less likely.

Keywords: Focal cortical dysplasia type IIIc, encephalomalacia, vascular malformation, acquired FCD

Introduction

Focal cortical dysplasia (FCD) is known to occur in association with a principal lesion (e.g., injury, epileptogenic tumor, and vascular malformation), usually located adjacent to or affecting the same cortical area/lobe; such lesions are uncommon. These unique lesions were newly introduced as FCD type III in the ILAE 2011 classification system of FCDs, and four variants (FCD type IIIa - IIId) have been proposed based on the associated principal lesion [1]. The etiology and pathogenesis remain to be elucidated, but likely to be an acquired phenomenon. Of these variants, FCD type IIIc refers to cortical lamination abnormalities when associated with vascular malformations (e.g., cavernomas, arteriovenous malformations, leptomeningeal vas-

cular malformations, telangiectasias, and meningoangiomatosis).

Histologically, FCD type IIIc is characterized by alterations in architectural or cytoarchitectural composition adjacent to vascular malformations listed above [1]. By MRI analysis, FCD type IIIc is usually easy to detect and comprises a broad spectrum of significantly distorted cortical gray matter and associated vascular malformations [2]. Several such examples have been reported to date in the literature; some were described (almost) exclusively with radiological features only [3-5], and others had detailed histological confirmation [6-8]. The principal lesion in the former group included arterial or venous malformation, while that of the latter was a cavernous angioma.

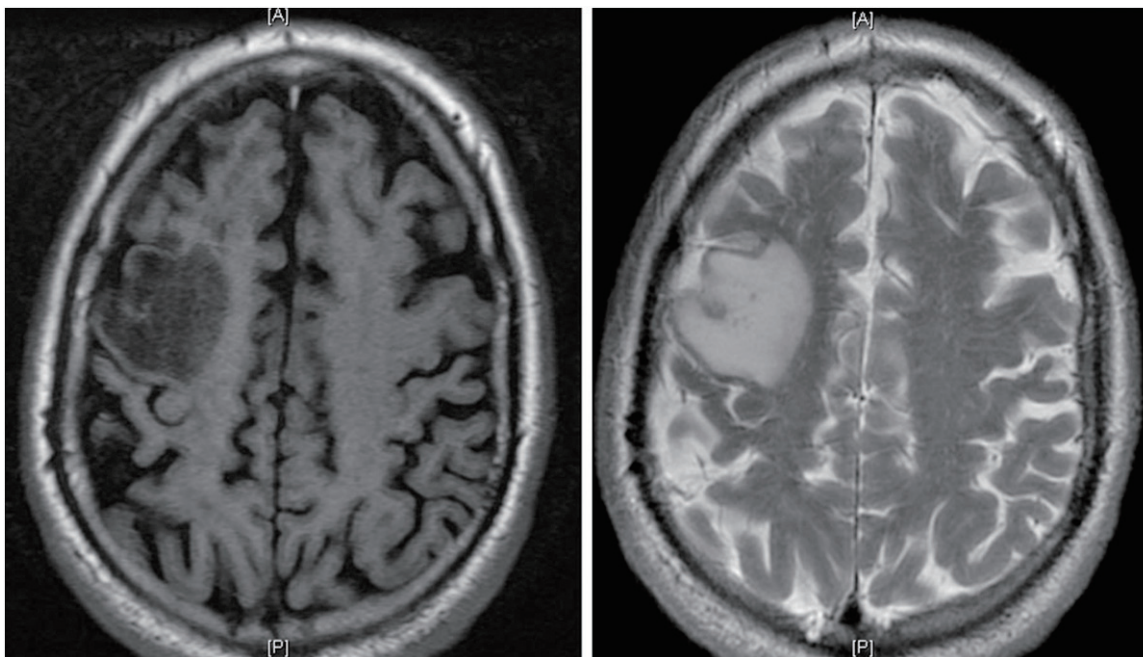


Figure 1. MR imaging (left: T1-weighted, right: T2-weighted image): Noncontrast MR imaging shows an intra-axial mass with low and high signal intensity on T1 and T2 weighted images, respectively, in the right frontal convexity. The lesion appears to be predominantly involving the subcortical area.

Here, we report a very rare case of encephalomalacic dysplastic lesion associated with vascular abnormalities, with presentation as a mass lesion in an elderly man. To our best knowledge, no other such cases have been reported to date.

Case report

The patient, a 75-year-old Caucasian man, presented with a seizure and left-sided weakness. MRI (without contrast) showed an intra-axial mass at the right frontal convexity, 4 cm in maximum diameter (**Figure 1**). The abnormality was mainly subcortical, with a smaller cortical component. No angiographic study was performed. Electroencephalogram demonstrated 2 to 3 Hz alpha activity predominantly in the right frontal region, but through most of the right cerebral hemisphere, excluding the occipital lobe. There were no other spikes or other focal epileptiform abnormalities.

His past medical history was significant for coronary artery disease (status post 4-vessel bypass surgery), atrial fibrillation, hypertension, hyperlipidemia, uncontrolled type 2 diabetes mellitus, gout, chronic renal disease, melanoma, and bladder cancer.

Craniotomy was performed for excision of the suspected neoplasm. At surgery, thickened gyri with red-gray discoloration were observed.

Postoperatively, he had a seizure and significant hemiparesis of the left upper extremity.

Pathologic findings

The surgical specimen was received as a single, intact piece of brain tissue, measuring 3.5 x 2.2 x 1.5 cm. On cut sections, the cortex and underlying white matter showed blurred interface between the gray and white matter.

Histologically, the leptomeninges were thickened and fibrotic, and meningeal blood vessels showed marked medial thickening with muscular hyperplasia, collagen deposition, and adventitial fibrosis affecting the larger and medium-sized arteries (**Figure 2A**). These changes are not typical of atherosclerosis. There was luminal occlusion of some of the larger vessels, with up to 50-60% luminal compromise. This feature also extended to some of the smaller parenchymal blood vessels. There were occasional occluded blood vessels with recanalization. A remarkable feature was the ectatic and dilated appearance of many of the brain parenchymal vessels, some with markedly hyalinized

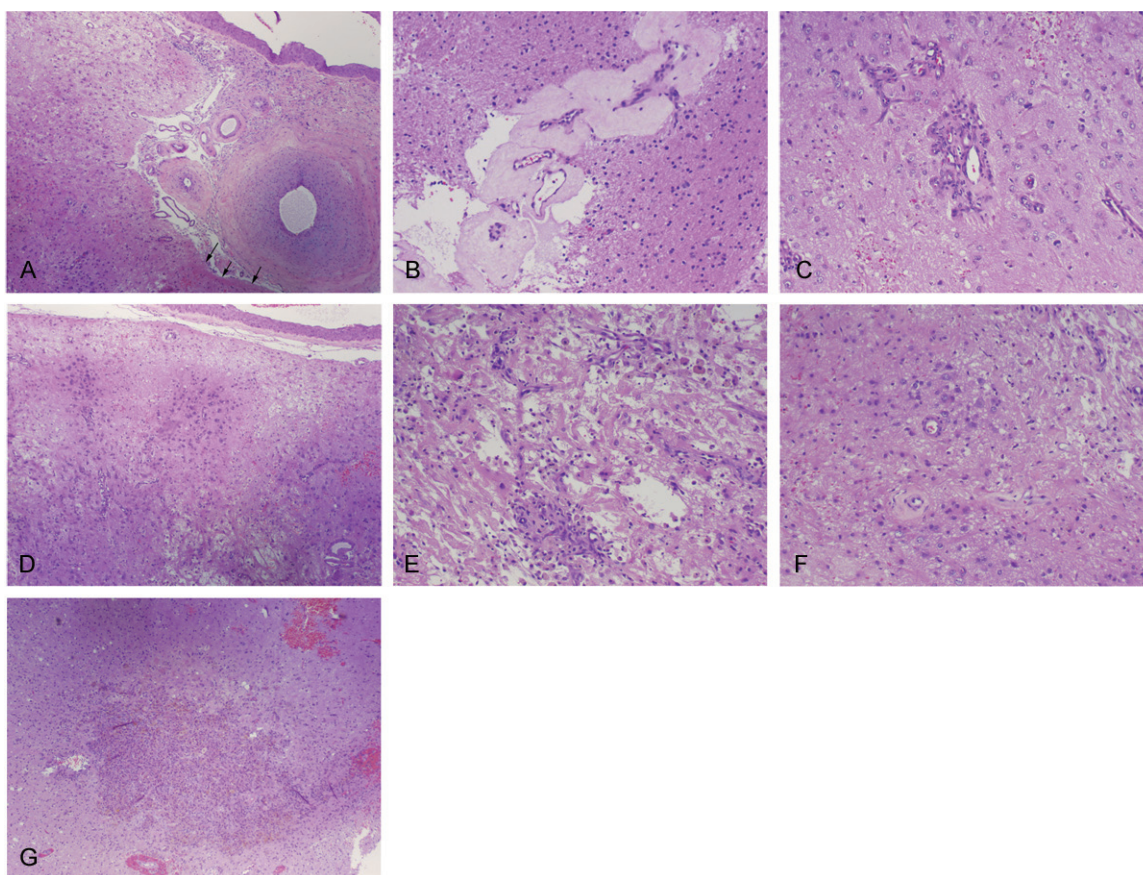


Figure 2. Histological findings (H&E stain): A: In the thickened and fibrosed leptomeninges, abnormal larger and medium-sized arteries with markedly thickened media are present. The cortex shows extensive astroglia with Chaslin's subpial gliosis (arrows). B: Ectatic blood vessels with markedly thickened hyalinized walls are present in the white matter. C: In the cortex, "glomeruloid" capillaries surrounded by abnormal neurons with dyslamination are noted along with astroglia. D: The cortex shows irregular areas of encephalomalacia, with intervening, almost nodular regions of "preserved" cortex. E: High power view of the cortical areas of encephalomalacia shows marked rarefaction with prominent astroglia, capillary proliferation, and scattered macrophages. F: High power view of the nodular regions of "preserved" cortex shows nodular collections of dysplastic maloriented neurons surrounded by marked astroglia. G: A nodular aggregate of macrophages in the edematous and rarefied white matter.

and thickened walls primarily in the white matter (**Figure 2B**), and several showed clusters (almost glomeruloid) of new capillary vessels of variable size (**Figure 2C**). There were focal perivascular lymphocytic infiltrates, but there was no evidence of a vasculitic process. Beta-amyloid immunostain (clone 6F/3D; Dako; prediluted) revealed no amyloid angiopathy, although moderate numbers of cored and diffuse amyloid plaques were identified in the cortex.

The cortex showed transition from normal, laminar cortical architecture to marked architectural abnormality with irregular areas of encephalomalacia, with intervening, almost nodular regions of "preserved" cortex (**Figure**

2D, 2E). These regions consisted of large clusters and aggregates of dysplastic maloriented neurons with thick dendritic processes (**Figure 2F**). Phosphorylated neurofilament protein (H subunit) immunostain (clone RMdO-20, Zymed, 1:80 dilution) highlighted maloriented axons and the thick dendritic processes (**Figure 3**). Severe diffuse astroglia of both gray and white matter was seen; there was also Chaslin's subpial gliosis. Also noted were few small areas of nodular macrophage aggregates in the white matter (**Figure 2G**). CD68 immunostaining (clone KP-1; Ventana; prediluted) revealed variable foamy macrophage infiltration in the encephalomalacic areas as well as diffusely increased microglia. No neoplastic component was found.

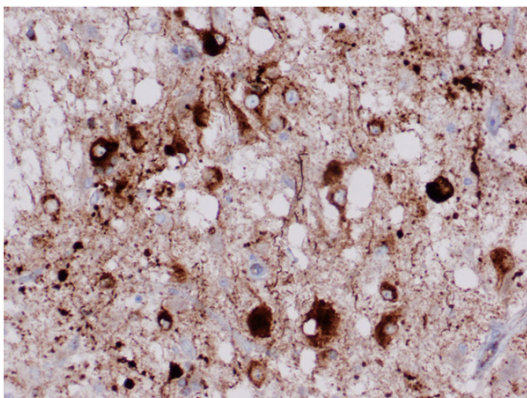


Figure 3. Immunohistochemical findings. Phosphorylated neurofilament protein antibody highlights an aggregate of dysplastic maloriented neurons with thick dendritic processes in the cortex.

Discussion

We report histopathological evidence of FCD coexisting with a very unusual vasculopathic process in an elderly man. This peculiar vasculopathy is characterized by a broad range of vascular abnormalities that include marked medial thickening predominantly of leptomeningeal arteries with significant luminal compromise, ectatic and dilated parenchymal vessels with markedly hyalinized and thickened walls (predominantly in the white matter), and “glomeruloid” clusters of new capillaries in the cortex. The medial thickening was composed of muscular hyperplasia and collagen deposition along with adventitial fibrosis, and these histological features are reminiscent of fibromuscular dysplasia (FMD). FMD, by definition, is a non-inflammatory and non-atherosclerotic arteriopathy predominantly involving small- and medium-sized vessels (of the middle-to-distal portions of the arteries) and is known to most frequently affect renal arteries. The extracranial cerebrovascular circulation (*i.e.*, carotid and vertebral arteries) is the second most commonly involved by this disease cases [9]. While intracranial involvement is very rare, it is one of uncommon causes of stroke in children. Leptomeningeal vessel involvement is probably rarer, and Arsene *et al.* found one case (a 78 year-old man) of cryptic FMD in the leptomeningeal vessels in their series of 100 consecutive autopsies [10]. Given the presence of a wide range of histopathologies in this patient’s vasculopathy, FMD is unlikely. For definitive exclusion, angiographic studies are required to

ensure that typical angiographic findings are absent. Glomeruloid capillaries were also found in the spectrum of vasculopathy in our case. Recently, glomeruloid microvascular changes have been reported in patients with *filamin 1* mutation, characterized phenotypically by bilateral periventricular nodular heterotopia [11]. Histologically, these lesions exhibit a compact tufted collection of multiple small lumina of similar size separated by circular walls that are thicker than those of normal capillaries [11]. Glomeruloid capillaries in our case were obviously different histologically from those seen in *filamin 1* mutation cases in terms of the absence of compactness, variability of capillary size, and thinner capillary walls. The etiology of this wide range of vasculopathic process remains uncertain; however, given the presence of multiple cardiovascular risk factors, some might consider that this process may be secondary to multiple ischemic insults/infarcts of varying degrees (*i.e.*, secondary vascular change) rather than primary vascular pathology. This possible etiology cannot be completely excluded, but given the presence of markedly unusual vasculopathies, a primary vascular pathology is favored. Angiographic studies may be of help in narrowing down the possible etiologies.

FCDs occurring in association with a principal lesion have been newly introduced as FCD type III in the ILAE 2011 classification system of FCDs [1]. However, these dysplastic changes had long been recognized, primarily in the pediatric epilepsy population in which ischemic/disruptive insults occur to the developing brain, before such lesions were formally incorporated into the new ILAE 2011 classification. In addition, we also reported FCD associated with Rasmussen’s encephalitis, which is currently classified as FCD type IIId according to the ILAE 2011 classification, in all 7 cases examined [12]. Clinically, histological identification of both co-existing lesions within the surgical specimen is important since it may help explain some failures in seizure control after lesionectomy of the principal lesion, especially in cases with a long-standing history of intractable epilepsy [7].

Of the four variants of FCD type III, FCD type IIIC is defined as cortical lamination abnormalities associated with vascular malformations, while FCD type IIId is associated with other lesions acquired during early life. We consider that our

case represents FCD type IIIc, but if all the lesions are the result of ischemia, it is not possible to classify this lesion by the current classification scheme, since the ischemic insults in FCD type IIIc are supposed to be acquired during early life.

A total of 4 cases of histologically confirmed FCD type IIIc have been reported to date [6-8], and all presented with seizures/epilepsy and contained a cavernous angioma as the principal lesion. All patients were adult males with a mean age of 36.8 years. One report suggested a possible common underlying developmental cause or process as contributing to this coexistence [8]. To our best knowledge, cases of FCD type IIIc with a very peculiar vascular pathology as described in our case have not been previously reported. We interpreted the cortical and subcortical encephalomalacic features to be presumably "secondary" to the underlying/associated vascular pathology. Moreover, this case may represent "acquired" FCD. It is possible that this patient had a preexistent cortical dysplasia with secondary ischemic changes; however, given the absence of previous history of seizure, this appears less likely. On the other hand, it is very possible that FCD type III lesions are caused by the seizures or by the lesion causing seizures, given that they are found, by definition, in association with a principal epileptogenic lesion nearby. Further studies with experimental animal models are required to prove causality of FCD as a result of a principal lesion and/or seizures.

Disclosure of conflict of interest

None.

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