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Solitary Cortical Tubers

David DiPaolo and Robert A. Zimmerman

Summary: We report two cases of solitary cortical tubers not associated with tuberous sclerosis and having an appearance simulating neoplasm in two patients presenting with seizures. CT showed solitary, hyperdense frontal lobe lesions in both patients. MR revealed a lesion hyperintense on both T1- and T2-weighted images in one patient and a heterogeneous mass with a target appearance in the other. Histologically, the lesions were consistent with cortical tubers.

Index terms: Sclerosis, tuberous; Brain, abnormalities and anomalies

Cortical/subcortical tubers are a common radiographic manifestation of tuberous sclerosis, one of the more common neurocutaneous syndromes. The typical appearance of a tuber on computed tomography (CT) is that of a hypoattenuated lesion in a cortical/subcortical location with or without focal gyral expansion. They may show calcification on CT in as many as 50% of cases and may also enhance (1). Magnetic resonance (MR) imaging is the better imaging test for displaying tubers, which are typically hypointense or isointense centrally on T1-weighted images and hyperintense centrally on T2-weighted images (2). Tubers may enhance with gadolinium in about 3% to 4% of cases, and they often show adjacent hyperintense bands of white matter on T2-weighted images with a radial orientation on MR, extending from the ependyma through the cerebral mantle toward the cortex (2). Ninety-five percent of tubers are multiple, and 90% occur in the frontal lobes (3). Tubers can have an atypical appearance and, when solitary in a patient without other features of tuberous sclerosis, may be confused with neoplasia. The variability in clinical expression of tuberous sclerosis recently has been appreciated (4–6); many formes frustes exist. We present two cases of solitary cortical tubers simulating neoplasm in patients who presented without a clinical diagnosis of tuberous sclerosis.

Case Reports

Case 1

A.B., an 8-month-old boy, presented with a 1-month history of seizures. There was no family history or clinical stigmata of tuberous sclerosis. Electroencephalogram (EEG) was reported as normal. The patient was treated with phenobarbital. MR performed at an outside institution (Fig 1A) showed a heterogeneous right frontal lobe lesion. On T1-weighted images, the lesion had a peripheral rim of increased signal intensity, consistent with calcification, and on T2-weighted images, the lesion showed decreased signal, also consistent with calcification. There was focal expansion of the overlying gyrus. The surrounding white matter in the right frontal lobe was hyperintense (Fig 1B). CT showed a densely calcified right frontal lobe mass (Fig 1C). The surrounding white matter had slight hypoattenuation.

The differential diagnosis included calcified tumor, such as oligodendroglioma, ganglioglioma, astrocytoma. A calcified tuber of tuberous sclerosis was suggested, but there were no other cortical or subcortical lesions, and no subependymal nodules were present. Surgical resection was performed. Histologic examination revealed an abnormal cortical pattern. The expected laminar arrangement of the cortex was replaced by a mixture of large neurons and giant cells with a pale, ground-glass cytoplasm, eccentrically placed nuclei, and prominent nucleoli. The abnormal cells extended into the white matter, which also was abnormal. The expected myelinated fibers in the white matter were replaced by a mixture of these giant cells. Gigantic neurons with coarse Nissl substance were noted. Some portions of white matter contained a dense network of glial fibers, and there was extensive calcium. No mitoses were seen. The glial fibrillary acidic protein stain was positive for this material in the smaller astrocytes but not in the giant cells. The vimentin stain showed intense staining of all cells, which appeared morphologically to be astrocytes, as well as some that looked like neurons. The final histologic diagnosis was cortical tuber.

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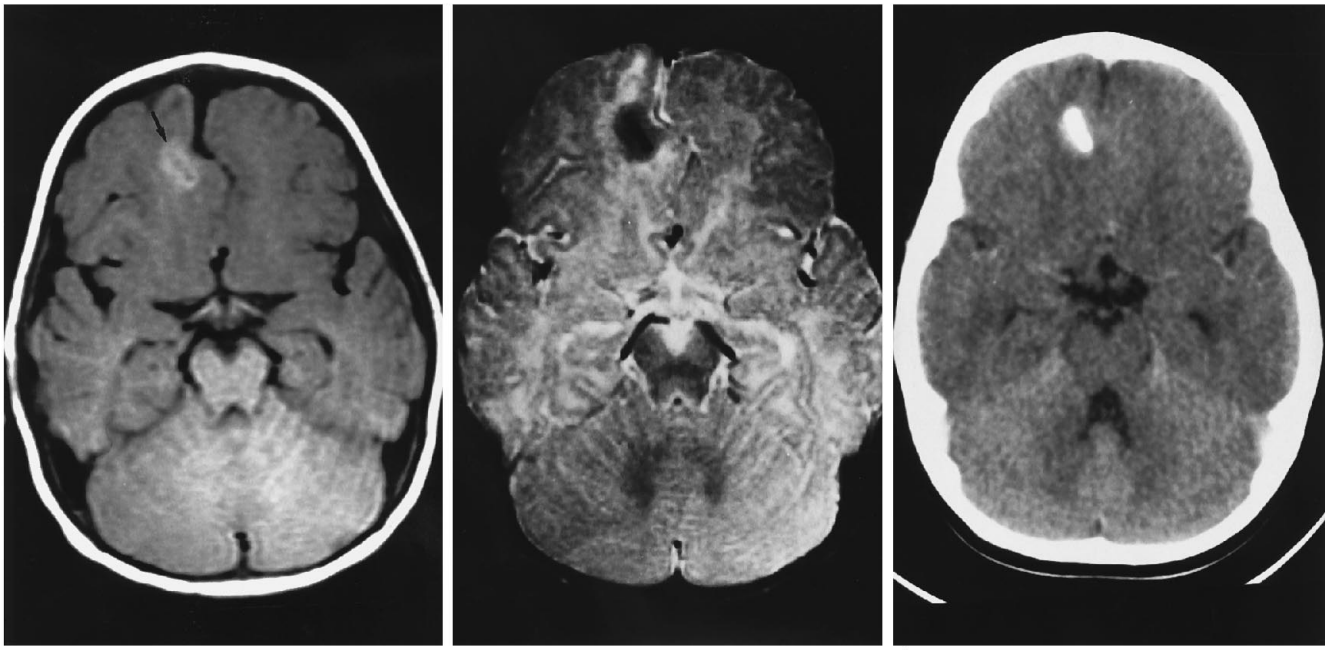


Fig 1. Patient 1. *A*, Axial T1-weighted image (800/20/2). Heterogeneous signal lesion in right frontal lobe (*arrow*). Increased signal is consistent with calcification.

B, Axial T2-weighted image (3000/80/1). Slight gyral expansion in right frontal lobe with oval area of decreased signal surrounded by hyperintense white matter.

C, CT with contrast enhancement. Calcified subcortical lesion in right frontal lobe with slight hypoattenuation of surrounding white matter.

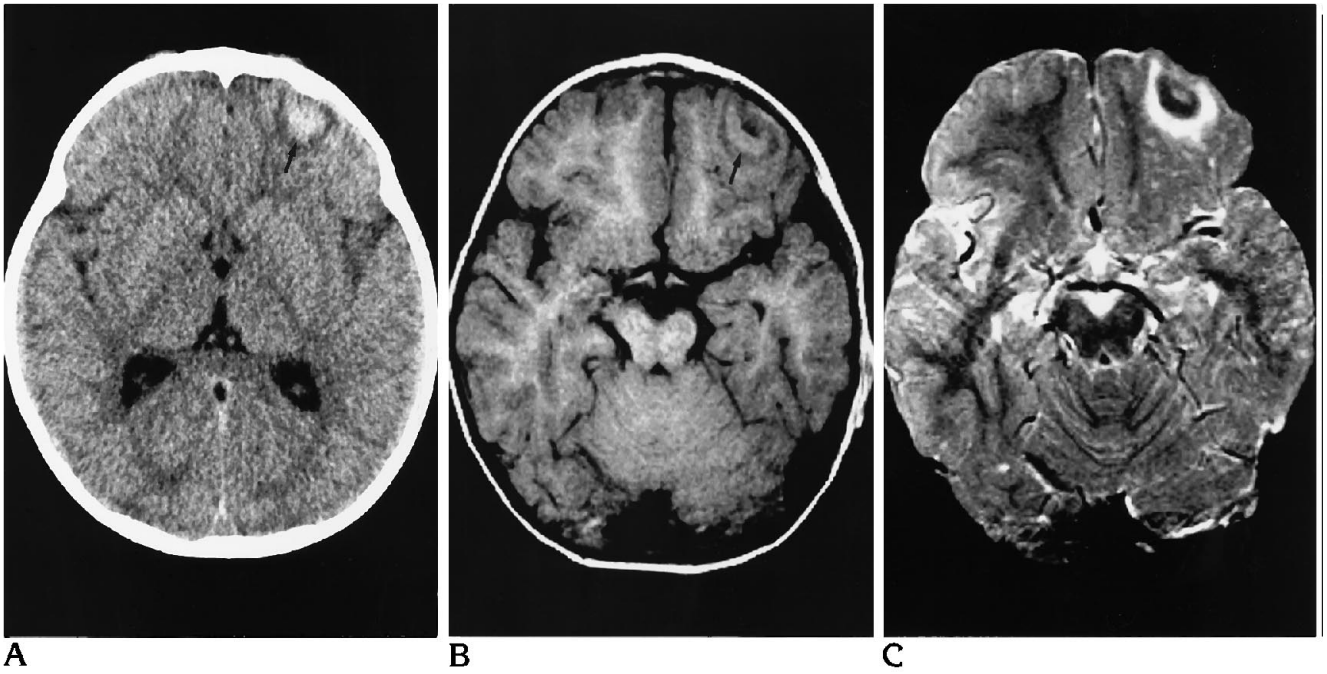
Case 2

A.F., a 22-month-old white boy, presented with a history of frequent seizures consisting of facial and eye twitching. He was being treated with anticonvulsants (phenobarbital and carbamazepine), which provided some relief. Physical examination by the neurosurgeon demonstrated no focal findings. Electroencephalography revealed an abnormal focus in the left temporal lobe.

CT demonstrated a well-defined ovoid lesion in the anterior inferior left frontal lobe, measuring approximately 2 cm in its longest dimension. It was hyperdense centrally with a hypoattenuated border (Fig 2A). No enhancement was appreciated after iodine administration. The differential diagnosis included low-grade tumor with calcification, such as oligodendroglioma, ganglioglioma, or possibly astrocytoma. A cortical tuber was considered a possibility.

MR examination revealed a heterogeneous left frontal lobe lesion with a ringlike configuration or "target" appearance, with a central area of decreased signal on T1-weighted images and increased signal on T2-weighted images (Fig 2B and C). On the T2-weighted images, the target appearance was particularly notable, with a central area of increased signal, an encircling ring of decreased signal, and a halo of increased signal. Peripheral enhancement was present on postcontrast study, and there was a subtle area of central enhancement in the lesion (Fig 2D).

The patient underwent surgical resection of the left frontal lobe mass. Histologically, the cellularity of both the gray and the white matter was increased. Although cortical cytoarchitecture was preserved, there were abnormalities in both neurons and glia. Many neurons had coarse amphophilic cytoplasm and recognizable filamentous material. A population of swollen cells of uncertain lineage with abundant, light pink, faintly granular cytoplasm and eccentrically placed, rounded, fascicular nuclei were present. Many of these cells contained thick, bizarre processes. An additional population of cells, which appeared to be astrocytes, had a homogeneous, eosinophilic cytoplasm and eccentrically placed nuclei containing finely granular chromatin. The white matter contained a polymorphic population of cells including the swollen, bizarre cells and astrocytes mentioned above. Numerous large neurons were identified. Glial fibrillary acidic protein staining revealed diffuse, moderate reactivity in both the gray and white matter, with strong reactivity of fibrillary astroglia. Immunohistochemical staining with vimentin demonstrated strong reactivity in the cytoplasm and bizarre processes of the swollen cells of indeterminate lineage. Nandrolone furylproprionate (NFP) staining showed strong reactivity in the cytoplasm and processes of neurons. Malorientation of neuritic processes was apparent with this stain. No calcification was seen histologically. The final diagnosis was cortical tuber.



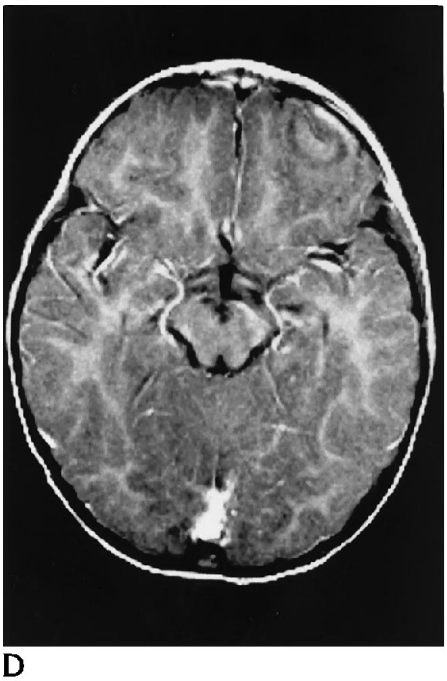


Fig 2. Patient 2. *A*, CT without contrast enhancement. Hyperdense cortical lesion (*arrow*) in left frontal lobe with surrounding low density.

B, Axial T1-weighted image (600/15/1). Heterogeneous left frontal lobe lesion with hypointense central core and a slightly hyperintense ring (*arrow*).

C, Axial T2-weighted image (3000/80/1). Target lesion in left frontal lobe with hyperintense core and outer ring and hypointense inner ring.

D, Axial T1-weighted image (600/22/1) with gadolinium. Slight peripheral enhancement and subtle central enhancement.

Discussion

Tuberous sclerosis is a hamartomatous disorder characterized by the clinical triad of mental retardation, seizures, and a cutaneous facial angiofibroma. Central nervous system manifestations include cortical/subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and ventriculomegaly (attributable to dysplastic ventricular enlargement or obstructive hydrocephalus produced by a subependymal giant cell astrocytoma causing obstruction at the foramen of Monro). Tuberous sclerosis has a pattern of autosomal dominant inheritance, and its incidence has been variously reported. Some of the older literature has quoted an incidence of approximately 1 in 100 000 to 1 in 150 000 (7). However, recent work suggests that the true incidence may be about 1 in 10 000 to 1 in 20 000 (8–10). There is growing awareness that many effaced forms

of the disease exist (4–6). It is possible that the only manifestation of tuberous sclerosis may be the presence of a solitary cortical tuber.

The cortical/subcortical tuber appears to represent a cluster of abnormal neurons whose migration has been perturbed (2, 11, 12). The lesion is centered on the gyrus and consists of giant cells, some of which resemble neurons; others, astrocytes. Myelin is decreased in the tuber, and dense fibrillary gliosis is present (8). Histologically, the lesions are benign, but tubers may enhance in about 3% to 4% of cases after gadopentetate dimeglumine administration (2). Tubers have no known malignant potential, so it is important to differentiate these masses from neoplastic processes. On MR, a cortical tuber typically shows focal gyral expansion, containing an area that is hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images (13). On long-repetition-time images, the adjacent white matter may contain hyperintense linear or curvilinear bands that extend from the ependyma of the ventricle to the tuber (2, 8). These radially oriented bands are a particularly helpful finding in the diagnosis of a cortical tuber, and they probably represent heterotopic cells, supporting the notion that disordered migration plays an integral role in, or is a trademark of, tuber formation. In young infants (younger than 4 to 6 months of age), the signal pattern of tubers is often reversed (ie, the lesions are bright on T1-weighted images and darker on T2-weighted images) (2).

Ninety percent of tubers occur in the frontal lobes (3). Calcification has been reported in as many as 50% of cases in some series (1). Calcification will affect the MR appearance of tubers. Dense calcification leads to decreased signal intensity on MR, particularly on T2-weighted images (14). Less dense calcification may be appreciated as hyperintensity on T1-weighted images (14), as was seen in our first case.

MR is better than CT for the evaluation of cortical tubers (2). On CT, tubers are typically hypoattenuating focal cortical or subcortical lesions with or without focal gyral expansion. CT may reveal calcification that is not apparent on MR. The hyperdense tuber seen in our second case did not demonstrate calcification on histologic examination, and the cause of the hyperdensity in this case is uncertain.

In the patient with tuberous sclerosis, tubers are multiple 95% of the time (3). In the roughly 5% of cases in which tubers are solitary, there may be other imaging findings, such as subependymal nodules, which are indicative of tuberous sclerosis, or there may be clinical stigmata or a family history of tuberous sclerosis. The cortical tubers of tuberous sclerosis are hamartomas, not neoplasms. Unlike the subependymal nodules, which may degenerate into subependymal giant cell astrocytomas in about 10% to 15% of patients, the cortical tubers have no neoplastic potential (2, 6). As such, they can be let alone. If a tuber corresponds to a seizure locus, resection may ameliorate symptoms.

A solitary cortical lesion in a patient without a clinical diagnosis of tuberous sclerosis may present a diagnostic dilemma. Expansion of the gyrus, frontal lobe location, hyperintensity, and adjacent white matter with radially oriented hyperintense bands on the long-repetition-time images are features suggestive of a cortical tuber. Enhancement may be misleading, because tubers occasionally have abnormality in the blood-brain barrier. With the growing realization that formes frustes of tuberous sclerosis are common, a solitary cortical tuber unassociated with other features of tuberous sclerosis should be a diagnostic consideration, given a masslike lesion in a cortical or subcortical location. In a patient without clinical evidence of tuberous sclerosis, recognition of the above features suggestive of a tuber could enable biopsy to be spared.

In the two cases reported here, the MR imaging features were atypical. The small cortical mass lesions had hyperintense peripheral rings on T1-weighted images, which were hypointense on T2-weighted images. In both cases, the abnormal signal was accentuated by surrounding hyperintensity. In both cases, on MR, there was no evidence of radially oriented bands extending from the ependyma to the cortical tuber. The locations of the lesions as demonstrated by both CT and MR were typical for tuberous sclerosis, as was the presence of calcification. However, without the presence of other tubers, subependymal nodules, radially oriented bands of white matter, or clinical stigmata of tuberous sclerosis, neoplasms, such as ganglioglioma, oligodendroglioma, or low-grade astrocytoma, could not be excluded, resulting in the need for surgical resection. In both patients, resection of the cortical tuber resulted not only in a histologic diagnosis but also in an amelioration of seizures. Thus far in the clinical and radiographic follow-up of our two patients,

additional signs of tuberous sclerosis have not developed.

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