RESIDENT & FELLOW SECTION

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# Clinical Reasoning: A 30-year-old woman with recurrent seizures and a cerebral lesion progressing over 2 decades

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## SECTION 1

A 30-year-old woman presented with a history of generalized tonic-clonic seizures since childhood, occurring for the first time at age 9. The initial diagnostic workup at age 13 demonstrated a distinctive calcified mass of the left frontal lobe on CT (figure, A). Together with a single facial nevus, the lesion was suspected to represent Sturge-Weber-like phakomatosis; however, the patient's clinical history and physical examination failed to reveal further evidence of a neurocutaneous syndrome. Neither MRI nor biopsy for histologic confirmation of the diagnosis was performed. At age 18 the patient was lost to follow-up at the children's hospital.

At age 30, the patient, who had been on permanent antiepileptic treatment with valproic acid, had a generalized seizure, prompting clinical and radiologic reassessment. The reported facial nevus was no longer detectable and the patient was free of neurologic symptoms or signs. CT scan of the head revealed calcified masses of the left and right frontal lobes (figure, B), with considerable progression when compared to the initial CT scans obtained 17 years before.

**Questions for consideration:**

1. What is the differential diagnosis?
2. What are suitable diagnostic measures?

GO TO SECTION 2

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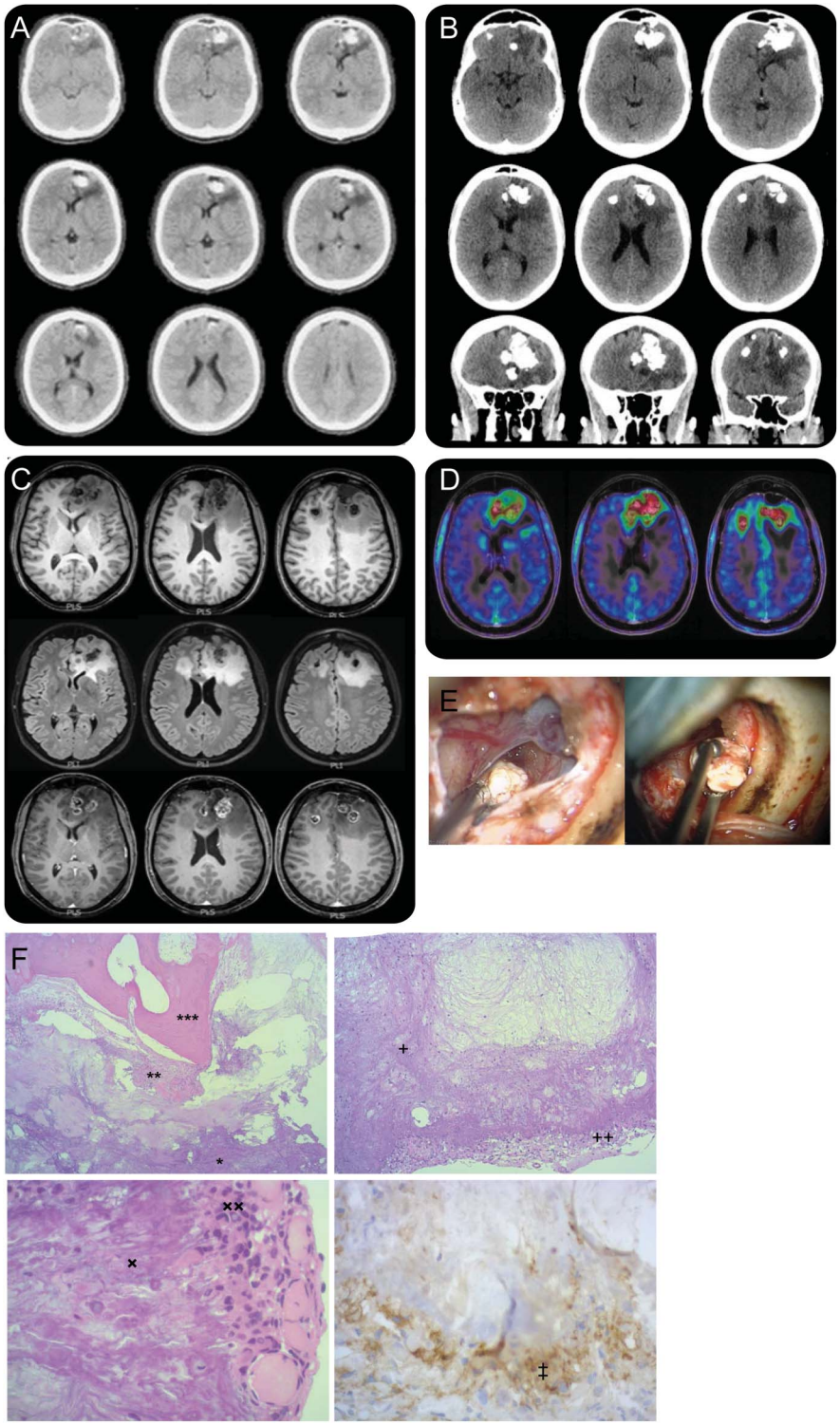
**Figure** Imaging findings, intraoperative view, and histologic analyses




CT scans of the head were obtained at age 13 years (A) and 30 years (B). (C) MRI findings on the axial T1- and T2/fluid-attenuated inversion recovery (FLAIR)–weighted sequences as well as axial contrast-enhanced T1 sequences. (D) Fluoro-ethyl-tyrosine-PET: red- and yellow-marked regions correspond to areas with high activity. (E) The intraoperative view during open biopsy of the mass. (F) At low magnification, the distinctive hypocellular appearance of calcifying pseudoneoplasms of the neuraxis is characterized by a core of amorphous basophilic material (*), loose bands of spindle cells (**), and, in this example, ossified tissue (***), considered a feature of more chronic lesions (upper left, hematoxylin & eosin [H&E], ×50). The vaguely chondroid to finely fibrillar core (+), somewhat resembling fibrocartilage, abuts a superficial rind of spindle to epithelioid cells (++ upper right, H&E, ×100). Coarse cords of lumpy, slightly fibrillar matrix (x) appear to radiate toward a cortical layer of epithelial-like cells with occasional nuclear pseudoinclusions (xx lower left, H&E, ×200). The epithelioid cells (‡), presumably of meningothelial origin, label epithelial membrane antigen (lower right, epithelial membrane antigen, ×200).

## SECTION 2

In the absence of significant clinical findings, the radiologic differential diagnosis based on CT scans is broad, including various primary and secondary brain tumors. Neoplasms with dense calcifications include, among others, oligodendroglioma, ganglioglioma, and meningioma. Vascular pathologies including cavernous malformations or aneurysms and infectious lesions with calcifications such as tuberculosis must be considered. Furthermore, Sturge-Weber syndrome and other neurocutaneous disorders can be associated with cortical calcifications. More advanced imaging techniques may be helpful to allow for a more precise diagnosis. An MRI scan confirmed the bifrontal masses with distinctive signal alterations on T1- and T2/fluid-attenuated inversion recovery (FLAIR)–weighted sequences of the surrounding brain parenchyma interpreted as chronic demyelinating and gliotic changes rather than acute vasogenic edema, consistent with the slow progression of the lesion. Contrast-enhanced T1 sequences demonstrated intense contrast enhancement in the noncalcified regions of the lesion (figure, C). In order to assess the nature of the mass more precisely, $^{18}$F-fluoro-ethyl-tyrosine PET ($^{18}$F-FET-PET) was performed, which displayed marked enhancement of tyrosine uptake compatible with metabolically active tissue (figure, D).

**Questions for consideration:**

1. What is the interpretation of the MRI and PET findings?
2. How can the diagnosis be established?

GO TO SECTION 3

Overall, the imaging findings cannot be considered as typical of Sturge-Weber syndrome or any other neurocutaneous syndrome. However, the strong tyrosine uptake indicates metabolically active tissue and is suspicious for a malignant tumor. Based on these considerations, the decision was made to obtain a biopsy for histopathologic assessment. A microsurgical open biopsy was undertaken with neuronavigation guidance in a superficial isolated lesion including meningeal and cortical samples within high FET uptake and contrast enhancement (figure, E). On gross examination, the tissue was noted to have a gritty texture and contained white flecks. Histologic analysis revealed an unstructured hypocellular mass with an amorphous vaguely chondroid to finely fibrillar core, somewhat resembling fibrocartilage, surrounded by mature lamellar bone and a superficial rind of spindle to epithelioid cells (figure, F, upper panels). Coarse cords of lumpy, slightly fibrillar matrix appeared to radiate toward the cortical layer of epithelial-like cells. These plump cortical cells with nuclear pseudoinclusions (figure, F, lower left) were variably positive for epithelial membrane antigen compatible with meningothelial origin (figure, F, lower right). The MIB1 proliferation was low (<1%) and mostly restricted to the surface cells. Based on the above features and the absence of other elements suggesting a neoplastic process, the diagnosis of "calcifying pseudoneoplasm of the neuraxis" was rendered.

**DISCUSSION** Calcifying pseudoneoplasms of the neuraxis (CAPNONs) are rare lesions of the CNS, with few patients reported to date.[1–10] CAPNON can occur both intracranially and spinally without a predominant localization. It has been described in patients aged from 6 to 68 years with a preponderance of males.[3] The clinical symptoms and signs vary and depend on the localization of the mass, with seizures as the most frequent symptom if the lesion is located intracranially.[1,2] Of note, CAPNON is a descriptive diagnosis and the underlying pathologic process is largely unknown. By definition, CAPNON is a discrete hypocellular, chondrocalcific, occasionally ossified mass that is covered by a surface layer of epithelioid cells of presumed meningothelial origin. According to the current interpretation, a reactive rather than a hamartomatous lesion has been assumed.[2] Other authors have suggested that the lesion represents abortive bone formation[7] or an extremely rare variant of a very low-grade neoplasm.[8] CAPNONs present with distinctive imaging features, as is illustrated in our case. CT scans typically show a densely calcified lesion,[1] whereas MRI mostly reveals hypointense T1 and T2 signals with mild and inhomogeneous internal or rim contrast enhancement.[1,4]

The present case adds some novel aspects and is of particular interest because of the radiologic documentation covering a period of 17 years, which demonstrates that these lesions can grow over a very long period of time. Furthermore, this is the first report on the use of FET-PET in a patient with CAPNON. The MRI demonstrated marked contrast enhancement in the noncalcified peripheral regions of the mass and a distinct T2/FLAIR signal alteration (figure, C), which differs from other reports. Furthermore, our patient underwent an $^{18}$F-FET-PET scan, which displayed profoundly increased tyrosine uptake (figure, D); however, FET-PET has not been previously reported in patients with CAPNON. Of interest, the PET results suggest the presence of tissue with high activity. Together with the CT and MRI findings, this led to the initial assumption of a malignant tumor. However, the histopathologic features shown in our case did not support the diagnosis of a malignant tumor but displayed the characteristic features of CAPNON. The histopathologic differential diagnosis encompasses tumoral calcinosis as seen in neoplasms such as osteosarcoma, chondrosarcoma, meningioma, or even gliomas; however, histologic evidence of a neoplastic process was lacking. Alternatively, since the lesion could not be completely excised, another entity not sampled by the surgical procedure cannot be excluded.

Our patient had a long-standing history of seizures that spanned more than 20 years. The radiologic documentation covers 17 years and indicates a clear progression of the lesion within this period. Resection has been proposed as the most appropriate treatment for CAPNON.[3] However, large lesions as in our case may not be amenable to complete resection. Owing to the lack of larger series, the value of complete vs partial resection remains speculative. However, given the continuous growth of the mass in our patient, complete resection—if considered feasible without causing neurologic deficits—may be the preferred approach. Partial resection may help to reduce the mass effect and neurologic symptoms but may not prevent further growth. Because of the lack of any therapeutic approach other than surgery, complete resection may be the only option to prevent continuous growth of CAPNON as in our case. Another important aspect of surgery is the collection of tissue, which allows for histopathologic confirmation of CAPNON and the exclusion of other differential diagnoses.

The progressive growth pattern of the lesion in our patient and the high activity assessed by FET-PET challenge the view that CAPNON represents an entirely benign lesion, despite the lack of histologic signs of malignancy. Other treatment modalities in patients with nonresectable CAPNON have not been established so far and the potential benefit of medical treatment such as steroid administration or more aggressive approaches such as chemotherapy or irradiation needs further investigation.

## AUTHOR CONTRIBUTIONS

M.T., M.G., O.S., M.W., and P.R. managed the patient and collected clinical data. E.R. performed the histologic analyses. O.S. did the surgery. A.V. and A.B. performed and analyzed the imaging studies. M.T., E.R., M.W., and P.R. wrote the manuscript. All authors approved the manuscript.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## DISCLOSURE

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