

## Multiple Intracranial Arteriovenous Fistulas in Cowden Syndrome

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Cowden syndrome is a rare autosomal dominant disease. It is characterized by multiple noncancerous tumorlike growths called hamartomas, which typically are found in the skin, oral mucosa, thyroid, breast, and gastrointestinal tract. It carries with it a potential risk of malignant transformation, especially of the breast and thyroid. In 80% of the cases, the human tumor suppressor gene, phosphatase and tensin homolog (*PTEN*), is mutated in the germ line. We report a patient with Cowden syndrome who presented with generalized seizure and left anterior temporal hemorrhage and a nontraumatic subarachnoid hemorrhage due to multiple intracranial arteriovenous fistulas (AVFs). We discuss previous reports about vascular malformations in patients with Cowden syndrome and *PTEN* mutations. Importantly, we hypothesize that the production of multiple AVFs in our patient was associated with *PTEN* mutation. **Key Words:** Cowden syndrome—*PTEN*—brain hemorrhage—arteriovenous fistula.

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### Case Report

A 46-year-old man was admitted to our emergency unit with a generalized seizure. The patient had a history of headaches and tinnitus and was diagnosed previously with Cowden syndrome (CS) 12 years before admission. The polymerase chain reaction–single-strand conformation polymorphism DNA sequencing confirmed that a mutation had occurred in the phosphatase and tensin homolog (*PTEN*) gene. The physical examination revealed known clinical features of CS,<sup>1</sup> such as the presence of macro-

cephaly, papillomatous lesions in the oral mucosa, and acral keratosis. A cranial tomography showed an acute left anterior temporal hemorrhage associated with a left parasagittal subarachnoid hemorrhage. The magnetic resonance imaging and then the arteriography revealed multiple dural and epidural high-flow arteriovenous fistulas (AVFs), predominantly in the right hemisphere. These fistulas received blood flow mostly from all the extra- and intracranial arteries (please see Fig 1). The causes of secondary intracranial AVFs, such as cerebral vein thrombosis or prothrombotic conditions, were ruled out. The patient had no history of head trauma or neurosurgical procedures. He was treated with 5 sessions of selective embolization. Few months later, the patient developed a refractory epilepsy and a rapidly progressive dementia. He died because of severe status epilepticus.

### Discussion

CS (OMIM#158350)<sup>2</sup> or multiple hamartoma syndrome is a rare disease characterized by multiple

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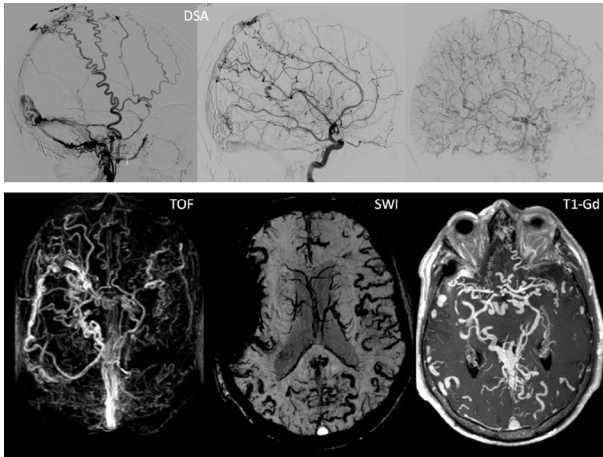
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**Figure 1.** DSA: internal and external carotid evaluation showed multiple fistulas. Axial views of magnetic resonance imaging, venous TOF, SWI, and T1-Gd confirmed the massive dilatation of cerebral veins, in relation to the fistulas. Abbreviations: DSA, digital subtraction angiography; SWI, susceptibility-weighted image; T1-Gd, T1 after gadolinium; TOF, time of flight.

hamartomatous lesions, especially of the skin, mucous membranes, brain, breast, thyroid, and colon. In some tissues, the hamartomas are associated with an increased risk of malignancy.<sup>1,2</sup> Verrucous skin lesions of the face and limbs, cobblestone-like papules of the gingiva and buccal mucosa, and multiple facial trichilemmomas are leading findings,<sup>1</sup> and also hamartomatous polyps of the colon and other regions. Approximately 80% of CS patients are caused by a mutation in the *PTEN* gene.<sup>2</sup> *PTEN* is a germline tumor suppressor gene that regulates cell division, angiogenesis, and proliferation.<sup>3</sup> Mutations in the *PTEN* gene have been associated also with Bannayan–Riley–Ruvalcaba syndrome (BRRS), Lhermitte–Duclos syndrome, and Proteus/Proteus-like syndrome.<sup>2</sup> CS and BRRS share some clinical characteristics and Marsh et al<sup>4</sup> suggested that the spectrum of disorders be referred to as “*PTEN* hamartoma tumor syndrome.”

Vascular malformations in CS are not well known<sup>5</sup>; however, they are common in *PTEN* hamartoma tumor syndromes.<sup>4</sup> Tan et al<sup>6</sup> identified vascular anomalies in 14 out of 26 pediatric patients with BRRS or CS and described anomalies in venous development in 8 of 9 patients in whom a brain magnetic resonance imaging was performed. Lok et al<sup>7</sup> found vascular abnormalities in 6 (30%) of 20 patients with CS; 5 cases of venous angioma and 2 cavernous angiomas (1 associated with venous angioma). Nevertheless, multiple intracranial fistulas in patients with *PTEN* mutations have been described only in a pediatric patient with BRRS.<sup>6</sup> We reviewed MEDLINE, Orphanet,

and OMIM databases, but we did not find cases of multiple AVFs in an adult with CS.

Most authors suggest that the high prevalence of vascular malformations in patients with CS is due to the loss of the regulatory angiogenic function of the *PTEN* gene.<sup>8</sup> This gene codes for a protein with antiangiogenic properties, which is expressed in the vascular smooth muscle, and regulates the formation of new vessels by suppressing vascular endothelial growth factor expression.<sup>5</sup> Cerebral AVF may be associated with the breakdown of auto-regulation of the dural microvascularization and the activation of the angiogenic factor.<sup>9</sup> In our patient, known causes of cerebral AVF<sup>9</sup> were ruled out and we cannot give any clear explanation. We hypothesized that finding multiple intracranial AVF in this patient is likely to be associated with the loss of the angiogenic function of the *PTEN* gene.

In conclusion, our patient provided evidence that CS may be associated with the development of intracranial vascular malformations. The main mechanism is related likely with the loss of the angiogenic regulatory function of the *PTEN* gene. More studies are needed to confirm the possible relationship between intracranial vascular malformations and the *PTEN* mutation.

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## References

1. Pilarski R. Cowden syndrome: a critical review of the clinical literature. *J Genet Couns* 2009;18:13-27.
2. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: {158350}: {03/14/2016}: World Wide Web URL:<http://omim.org/>.
3. Liaw D, Marsh DJ, Li J, et al. Germline mutations of the *PTEN* gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997;16:64-67.
4. Marsh DJ, Kum JB, Lunetta KL, et al. *PTEN* mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. *Hum Mol Genet* 1999;8:1461-1472.
5. Turnbull MM, Humeniuk V, Stein B, et al. Arteriovenous malformations in Cowden syndrome. *J Med Genet* 2005;42:e50.
6. Tan WH, Baris H, Burrows P, et al. The spectrum of vascular anomalies in patients with *PTEN* mutations: implications for diagnosis and management. *J Med Genet* 2007;44:594-602.
7. Lok C, Viseux V, Avril MF, et al. Brain magnetic resonance imaging in patients with Cowden syndrome. *Medicine* 2005;84:129-136.
8. Farooq A, Walker LJ, Bowling J, et al. Cowden syndrome, tumour review. *Cancer Treat Rev* 2010;36:577-583.
9. Ha SY, Kwon YS, Kim BM, et al. Clinical and angiographic characteristics of multiple dural arteriovenous shunts. *AJNR Am J Neuroradiol* 2012;33:1691-1695.