

Spinal Extradural Arteriovenous Fistula with Cowden Syndrome: A Case Report and Literature Review Regarding Pathogenesis and Therapeutic Strategy

Jun Takei,¹ Satoru Tochigi,¹ Masami Arai,² Toshihide Tanaka,¹ Ikki Kajiwara,¹ Keisuke Hatano,¹ Daisuke Ichinose,¹ Hiroki Sakamoto,¹ Yuzuru Hasegawa,¹ Toshihiro Ishibashi,³ Satoshi Tani,³ and Yuichi Murayama³

We report the case of a patient with a spinal extradural arteriovenous fistula (AVF) associated with Cowden syndrome (CS) that was successfully treated by endovascular surgery. CS is an autosomal dominant disorder associated with diverse symptoms caused by a deleterious mutation in the phosphatase and tensin homolog (*PTEN*) gene. A 67-year-old woman was diagnosed with CS based on her medical history of multiple cancers for which she underwent abdominal surgery, macrocephaly, Lhermitte-Duclos disease, and facial papules. Her genetic testing demonstrated a *PTEN* mutation. She presented with progressive paraparesis and her MRI of the thoracolumbar spine showed the spinal cord edema along with flow voids. A spinal angiogram demonstrated a spinal extradural AVF with the perimedullary drainage. The AVF was successfully treated by endovascular surgery. The *PTEN* mutation can accelerate angiogenesis; thus, vascular anomalies are one of the diagnostic criteria of CS. However, only two cases of vascular anomalies involving the spinal cord in patients with CS have been reported previously. As the present case, both cases had a history of abdominal or retroperitoneal cancer. The *PTEN* mutation accompanied with abdominal surgery might have caused this vascular anomaly as the consequences of venous congestion around the thoracolumbar spine. A spinal extradural AVF should be considered in patients with CS who present with myelopathy, especially when the patient has a history of abdominal or retroperitoneal surgery. Regarding the treatment strategy, endovascular surgery should be considered because surgical insult could prompt secondary vascular anomalies resulting from neovascularization due to the *PTEN* mutation.

Keywords: central nervous system vascular anomalies, Cowden syndrome, Cowden disease, dural arteriovenous fistula, *PTEN* hamartoma tumor syndrome

Introduction

Cowden syndrome (CS) is a rare autosomal dominant disorder associated with multiple hamartomas and a high risk of the development of malignant tumors. The physical characteristics of the disorder are macrocephaly and pathognomonic mucocutaneous lesion, including trichilemmomas and papillomatous papules. Approximately 80% of patients with CS have a phosphatase and tensin homolog (*PTEN*) mutation.¹ When a *PTEN* mutation is identified by genetic analysis, the patient is diagnosed with *PTEN* hamartoma tumor syndrome (PHTS). PHTS includes CS, Bannayan–Riley–Ruvalcaba syndrome (BRRS), Proteus syndrome, and Proteus-like syndrome.²

Vascular anomalies, including arteriovenous malformations and cavernous malformations, have also been reported as symptoms of PHTS, particularly in patients with CS and BRRS.³ However, vascular anomalies involving the spinal cord are extremely rare. Herein, we report a case of a thoracolumbar spinal extradural arteriovenous fistula (AVF) in a patient with CS that was successfully treated by endovascular surgery.

Case Report

A 67-year-old woman presented with a chief complaint of progressive motor weakness of the lower extremities for the past 4 days and was referred to our emergency department. She had a medical history of macrocephaly, Lhermitte-Duclos disease in the left cerebellar hemisphere, and face trichilemmomas. Furthermore, she had also undergone surgery for breast cancer and advanced cecal cancer. Therefore, she had been clinically diagnosed with CS according to the National Comprehensive Cancer Network diagnostic criteria with direct sequencing of *PTEN* by polymerase chain reaction (PCR) revealing a missense mutation: p.G129V in exon 5. The neurologic examination demonstrated grade 1 spastic paraparesis in manual muscle testing (MMT) with sensory disturbances at the level of the seventh thoracic dermatome bilaterally. She had urinary incontinence upon admission. MRI of the thoracolumbar spine showed edema extending from T8 to the conus medullaris with flow voids along the dorsal side of the thoracic cord (Fig. 1A). A spinal angiogram (Artis zee BA Twin, Siemens, Munich, Germany) demonstrated a spinal extradural AVF with the perimedullary drainage. The fistula was supplied by the dorsal somatic branches from the bilateral L1 and left L2 segmental arteries,

¹Department of Neurosurgery, Jikei University Kashiwa Hospital, Kashiwa, Chiba, Japan

²Department of Clinical Genetic Oncology, the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan

³Department of Neurosurgery, Jikei University School of Medicine, Tokyo, Japan

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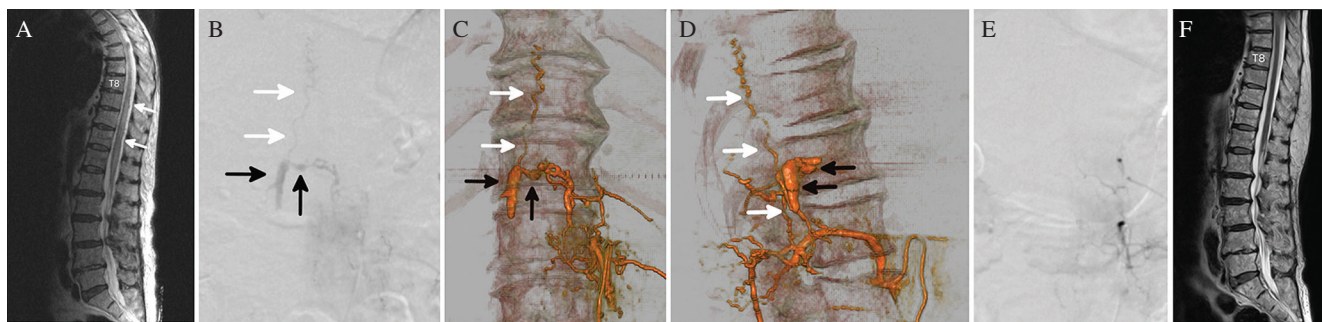


Fig. 1 (A) A T2-weighted MRI of the thoracolumbar level showing intramedullary hyperintensity (white arrows) extending from T8 to the conus medullaris with some dorsal perimedullary flow voids. (B) Spinal DSA, the left L2 injection, showing a spinal extradural AVF with an extradural venous pouch (black arrows) that drained into the perimedullary vein (white arrows). (C) A 3D rotational DSA, the left L2 injection, anterior-posterior view, showing the ventral venous pouch (black arrows) was connected to the perimedullary vein (white arrows). (D) 3D-rotational DSA, left L2 injection, lateral view, showing the relationship between the vascular and bony structures. (E) Spinal DSA, left L2 injection, showing the fistula and perimedullary vein were completely obliterated. (F) Spinal MRI T2-weighted images, 1 year after embolization, showing the resolution of the thoracic cord edema. MRI: magnetic resonance imaging, DSA: digital subtraction angiography, 3D: three-dimensional.

and they drained into the perimedullary vein via the right-sided epidural venous pouch (Figs. 1B–D). She underwent two-staged endovascular embolization. A microcatheter was successfully placed up to the distal part of the right L1 lumbar artery, and the shunt point as well as the venous pouch was completely embolized with 25% *n*-butyl-2-cyanoacrylate (Fig. 1E). Her symptoms gradually improved so that the motor examination of her lower extremities demonstrated grade 3 in MMT 30 days after the treatment. One year later, the fistula was not recanalized, and she was able to walk with a walker. An MRI of the thoracolumbar spine revealed resolution of the thoracic cord edema (Fig. 1F).

Discussion

The International Consortium diagnostic criteria for CS were created in 1996 based on clinical experience and case reports from the literature.⁴ According to the initial diagnostic criteria, vascular anomalies were not included. While case reports regarding PHTS have increased, PHTS turned out to represent vascular anomalies. Since the diagnostic criteria for PHTS was revised in 2013, vascular anomalies have been included as the minor criteria.³ However, vascular anomalies of PHTS usually occur in the soft tissues and skin.⁵ We reported the case of a spinal extradural AVF in a patient with CS with a missense mutation: p.G129V in exon 5. As summarized in Table 1, only three cases of vascular anomaly involving the spinal cord in patients with CS have been reported previously.^{6,7} Various *PTEN* mutations were shown in these cases. In our case, a PCR-direct sequencing of *PTEN* revealed a missense mutation: p.G129V in exon 5. This mutation is classified into variant of uncertain significance in the diagnosis of FALCO biosystems (Kyoto, Japan). Missense mutations are usually hard to identify as either deleterious or as an uncertain significant variant. Yet, this mutation has been reported previously as deleterious,⁸ and an in silico analysis demonstrated that the mutation likely negatively impacted the protein (polyphen2, SIFT, and Align-GVGD). In addition, since exon 5 of the *PTEN* gene encodes

the functional domain of the protein, mutations in this region may affect its phosphatase function.⁹ Although the *PTEN* gene is one of the most commonly mutated tumor suppressor genes in patients with cancer, *PTEN* mutations are also known to accelerate angiogenesis. The loss of *PTEN* functioning leads to overexpression of angiogenic factors such as vascular endothelial growth factor (VEGF).¹⁰ Therefore, the mutation was considered to elicit vascular anomalies with angiogenesis.

There was another factor of developing spinal extradural AVF in the present case. We speculated that spinal extradural AVFs tend to develop in patients with CS because of the venous congestion caused by abdominal surgery for associated malignant tumors. All reported cases had a history of cancers in the abdominal or retroperitoneal cavity accompanied with an extradural AVF at the lumbar level. Murakami et al. described seven cases of a spinal extradural AVF with a history of surgery.¹¹ Most secondary spinal extradural AVFs occurred after laminectomy. Meanwhile, there were two cases of spinal extradural AVFs following prostatectomy and resection of the abdominal aortic aneurysm. Thus, abdominal or retroperitoneal surgery might cause venous congestion around thoracolumbar spine, resulting in vascular anomalies particularly in patients with CS.

In terms of treatment strategy, Rangel-Castilla et al. classified spinal extradural AVFs into three types, of which type A was defined spinal extradural AVFs with the intradural venous drainage.¹² The therapeutic goal for type A spinal extradural AVF is occlusion of the intradural perimedullary vein and the epidural venous pouch. In our case, we performed the endovascular surgery for the following reasons. First, the extradural AVF composed of a single perimedullary drainer. Second, considering the genetic background of excessive angiogenesis, such as the *PTEN* mutation, direct surgery might have caused secondary vascular anomalies by the surgical insult itself. Sadahiro et al. reported a case of secondary dural AVF that developed in the cerebellar surface, together with the thickened dura mater

Table 1 Reported cases of spinal dural or extradural AVF in a patient with Cowden syndrome

Author	Age/ Sex	AVF location	Fistula level	<i>PTEN</i> mutation/ Locations	Past medical history	Symptoms and signs	Treatment	Outcome	Follow-up period
Wu et al. ⁶⁾	65/M	Spinal dural AVF	L3	c.37A>T/Exon 1	Prostate cancer	Lower limb weakness, dysesthesia, urinary retention	TAE	GR	4 months
Barreras et al. ⁷⁾	57/F	Spinal extradural AVF	L2, L4	Positive/Intron 3	Nephrectomy	Lower extremities weakness, numbness	TAE	MD	2 years
Present case	67/F	Spinal extradural AVF	L1, L2	p.G129V/Exon 5	Ileocecal resection	Paraplegia	TAE	MD	1 year

AVF: arteriovenous fistula, F: female, GR: good recover, M: male, MD: moderate disability, TAE: transarterial embolization.

containing abnormal vessels after brainstem cavernous angioma surgery in a patient with CS. Immunohistochemical findings of the removed dura mater revealed that the abnormal vessels were diffusely positive for VEGF, which might have resulted in neovascularization of the dura mater.¹³⁾ This fact may support our therapeutic strategy.

As mentioned above, patients with CS usually had surgical histories as a consequence of accompanied malignant cancers. A spinal extradural AVF could occur in patients with CS because of the abdominal venous congestion by surgical insults and the possibility of excessive neovascularization due to *PTEN* mutations. If type A spinal extradural AVF is found in patients with CS, endovascular surgery might have an advantage so as to avoid surgical insults.

Conflicts of Interest Disclosure

The authors have no conflicts of interest to declare.

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Corresponding author:

Jun Takei, MD, Department of Neurosurgery, Jikei University Kashiwa Hospital, 163-1 Kashiwashita, Kashiwa, Chiba 277-8567, Japan.

✉ j_tki@jikei.ac.jp