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A Longitudinally Extensive Myelopathy associated with Multiple Spinal Arteriovenous Fistulas in a patient with Cowden Syndrome: A Case Report

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ABSTRACT:

BACKGROUND CONTEXT: Cowden syndrome is an autosomal dominant syndrome characterized by multiple hamartomas and an increased cancer risk. It is associated with mutations in the phosphatase and tensin homolog (PTEN) gene that encodes a tumor suppressant phosphatase.

PURPOSE: To report an unusual case of multiple spinal epidural arteriovenous fistulas in a patient diagnosed with Cowden syndrome.

STUDY DESIGN: Case report

PATIENT SAMPLE: A 57-year-old woman

METHODS: We report the case of a 57-year-old woman with a history of multiple cancers with acute exacerbation of lower extremity weakness and numbness that had progressed over a month.

RESULTS: MRI showed abnormal signal in the thoracolumbar spinal cord with enhancement after contrast administration. A spinal angiogram confirmed the presence of multiple spinal epidural arteriovenous fistulas. Genetic testing confirmed the diagnosis of Cowden syndrome with a mutation in intron 3 of the PTEN gene.

CONCLUSIONS: Spinal vascular malformations occur in patients with Cowden syndrome, they can be multifocal and locally aggressive. It is important to raise the suspicion of Cowden syndrome in patients with spinal cord vascular anomalies and a history of multiple cancers, as the correct genetic diagnosis may have implications for management and cancer screening.

Key words: PTEN, Cowden syndrome, arteriovenous fistula, myelopathy, spinal cord.

INTRODUCTION

Cowden syndrome is an autosomal dominant syndrome characterized by the development of multiple hamartomas, an increased risk of certain malignancies including breast, cervical and thyroid cancer, and the presence of soft tissue and

visceral vascular abnormalities [12,16]. In almost 80% of the cases, mutations in the phosphatase and tensin homolog (PTEN) gene have been identified [16]. The PTEN gene encodes a tumor suppressor phosphatase located in chromosome 10q23.3, which has a role in cell cycle arrest, angiogenesis, and apoptosis [7, 21]. PTEN germline mutations are present in several cancer syndromes, including Cowden syndrome, Proteus syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Lhermitte-Duclos disease, disorders grouped under the name of PTEN Hamartoma-Tumor syndromes (PHTS) [7,12, 16, 27].

Vascular abnormalities such as hemangiomas, hamartomas, and soft tissue arteriovenous malformations (AVM) have been described in patients with PHTS [14, 19]; they are more common in patients with BRRS with varying location and severity. In Cowden syndrome, the vascular lesions are most frequently soft tissue hemangiomas [12, 18] while visceral AVMs are rare [24]. PHTS associated vascular abnormalities are even less frequent in the central nervous system (CNS), with only a few case reports of AVMs and cavernous hemangiomas [17, 20, 23]. Spinal cord vascular anomalies have rarely been described. We report an unusual case of longitudinally extensive myelopathy associated with multiple spinal epidural arteriovenous fistulas (SEAVF) in a patient previously diagnosed with breast, kidney and scalp carcinomas in the context of Cowden syndrome.

CASE REPORT

Presentation

A 57-year-old woman presented to the emergency department after sudden onset of weakness and urinary retention. The acute symptoms had been preceded by at least one month of progressive weakness and numbness in the lower extremities and a fall four days before admission due to abrupt weakness, which recovered spontaneously after three hours. She was treated initially with IV steroids for a presumed transverse myelitis (TM) but worsened overnight and was transferred to our institution for further evaluation. The patient had a previous history of invasive ductal breast carcinoma at age 41, which was treated with chemotherapy and radiation therapy. At that time, she was also found to have a clear cell carcinoma of the kidney treated by nephrectomy. At age 56, she was diagnosed with a squamous cell carcinoma of the scalp, which was surgically resected, as well as multiple benign colon polyps and type II diabetes mellitus. There was no family history of cancer. On admission**,** her general exam showed macrocephaly (head circumference: 59 cm) and multiple lipomas. The initial neurological exam revealed normal mental status and cranial nerves examination. Her motor exam demonstrated normal strength in upper extremities but paraparesis with overall strength of 1/5 (MRC) in all muscle groups of the lower extremities. She had patellar and Achilles areflexia, and a L1 sensory level. She had urinary incontinence on admission.

Basic hematology and electrolyte blood analyses were normal. The cerebrospinal fluid analysis showed 4 white blood cells, 13 red blood cells, normal glucose at 62 mg/dl, elevated protein at 116 mg/dl, negative gram stain and cultures. A brain MRI was normal. A MRI of the spine demonstrated a longitudinally extensive myelopathy characterized by centromedullary hyperintense signal from T5 to the conus medullaris

on T2-weighted sequences, with enhancement after gadolinium injection. Two separate epidural lesions with bony erosion were noted as well (Figure 1). A vascular myelopathy secondary to venous hypertension was suspected. She underwent spinal angiography, which revealed two separate SEAVFs at L2 and L4 (Figure 2). Both lesions were successfully treated by endovascular means, via transvenous (L4) and transarterial (L2) approaches.

Following treatment, the paraparesis slowly improved to an overall strength graded 3/5 in lower extremities. She was discharged to a neuro-rehabilitation facility, where she became able to walk with the aid of a walker. She continued to improve until 1 year later, when she suffered a sudden exacerbation of lower extremity weakness that left her paraplegic and without bladder control. She was re-admitted for evaluation and found to have a new enhancing thoracolumbar spinal cord lesion. A complete spinal angiogram showed no new or recurrent vascular malformation, but revealed the absence of normal perimedullary veins suggesting diffuse spinal venous thrombosis. She was again discharged to a rehabilitation facility. Two years later, she was able to walk with a walker, had regained partial bladder function, and had partially recovered sensation in her lower extremities.

Genetic testing and Cowden syndrome diagnosis:

Genetic testing was obtained given the patient history of multiple malignancies. Next generation sequencing (CancerNext-Expanded Panel, Ambry Genetics) was performed. A deleterious mutation (209+4_209+7delAGTA) was found in intron 3 of the PTEN

gene. This was consistent with PHTS and based on the clinical presentation is most consistent with Cowden syndrome.

DISCUSSION

Cowden syndrome is a rare autosomal dominant disorder characterized by macrocephaly, multiple hamartomas mostly located in soft tissues, and increased risk for malignancies such as breast, thyroid, endometrial, colorectal and renal cell carcinomas, generally manifesting by the age of 20 [7, 16]. The incidence of Cowden syndrome is approximately 1 in 200 000 [7]. Our patient was diagnosed with Cowden syndrome based on two major criteria, macrocephaly and breast cancer, and two minor criteria, lipomas and renal cell carcinoma [15].

Vascular anomalies have been reported in association with PHTS [8, 14, 18, 19, 24], most frequently soft tissue hamartomas in the lower extremities, less commonly in the upper extremities, trunk and neck [12]. Recent studies have demonstrated the presence of vascular anomalies in approximately 54% of patients with PTEN mutations, frequently intramuscular and associated with excessive ectopic fat [23]. On the other hand, vascular lesions such as arteriovenous malformations or fistulas (AVF) involving the CNS are rare. A case-series of 26 patients with PTEN mutations found only one patient with a brain AVM [23].

In Cowden syndrome in particular, AVMs and AVFs are rare when compared to other PHTS syndromes and, when present, they are mainly located outside the CNS [24]. 28% of pediatric patients with AVFs have associated genetic syndromes including PTHS [1, 25]. However, spinal AVMs or AVFs have rarely been described in association

with such genetic syndromes. To our knowledge, there have been only a few reports of PHTS-related spinal vascular disease, including a case of an extradural spinal hemangioma with Bannayan-Zonana syndrome [9], a paraspinal AVF with Lhermitte-Duclos disease [2], as well as a cervical paraspinal AVM [3] and a spinal dural AVF [26] in association with Cowden syndrome. The latter case was a 65-year-old man presenting similarly to our patient with progressive weakness, sensory abnormalities, and urinary retention. MRI demonstrated abnormal signal in the thoracolumbar spinal cord with enhancement after gadolinium administration; angiography confirmed the presence of an AVF [26].

Our patient had a deleterious mutation in intron 3 of the PTEN gene, while the only other reported case of AVF in Cowden syndrome had a mutation in exon 1 [26]. A mutation similar to our patient's was detected in a case of papillary thyroid cancer and cervical paraspinal AVM [3]. A review of vascular anomalies in 26 cases of PHTS, found only two patients with mutations in intron 3, one patient with a brain developmental venous anomaly, the other an intramuscular AVM in the left lower extremity [23].

PTEN has both lipid and protein phosphatase activity; the lipid phosphatase activity negatively regulates the PI3k/AKT signaling involved in many cellular functions, including cell growth and differentiation [22]. By inhibiting AKT signaling, PTEN is a negative regulator of cell cycle and apoptosis [21]. Alterations in exon 3 have been shown to reduce phosphatase activity essential for tumor suppression activity [1].

Interestingly, some of PTEN influenced pathways may also regulate vascular growth factors; a recent study showed that inhibition of PTEN expression induces proliferation

and migration of vascular smooth muscle cells [6]. Animal studies revealed an important role of PTEN gene in angiogenesis. In the zebrafish, haploinsufficiency of PTEN predisposes to vascular lesions such as hemangiosarcomas [4], while lacking functional PTEN results in hypervascularization and increased expression of *vegfaa*, a ligand of vascular endothelial growth factor (VEGF) receptors [5]. Another study corroborated the PTEN role in modulation of VEGF mediated signaling [10]. In chicken embryos, overexpression of PTEN inhibits angiogenesis [11], and appears to be involved in the control of vasculogenesis during development [13]. These results indicate that PTEN may act through different signaling pathways to influence different aspects of angiogenesis, which may explain the multiplicity of AVMs and AVFs in PTHS and in Cowden syndrome in particular.

CONCLUSION

To our knowledge, we present the first observation of multiple spinal epidural AVFs in Cowden syndrome syndrome associated with a mutation in intron 3 of the PTEN gene.

Our report emphasizes that PTHS must be suspected in patients presenting with spinal AVMs or AVFs and a history of multiple cancers, as establishing the correct genetic diagnosis has important implications for management and cancer screening.

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FIGURE LEGENDS

Figure 1. Spine MRI.

A, T2-weighted image, thoracic level, sagittal view, showing intramedullary hyperintensity from T5 down to the conus, most pronounced between T8 and T10; some dorsal perimedullary flow-voids are noted (small arrow), as well as an epidural mass with bone scalloping at L2 (large arrow). **B**, T1-weighted image after gadolinium injection, thoracic level, sagittal view, documenting spinal cord enhancement predominating between T8 and T10, and confirming the presence of an epidural lesion at L2 (large arrow). **C,** T2-weighted image, T8 level, axial view, showing intramedullary hyperintensity with a central pattern. **D**, T1-weighted image after gadolinium injection,

T8 level, axial view, showing enhancement of the posterior aspect of the spinal cord. **E,** T2-weighted image, lumbar level, sagittal view, demonstrating a second bone scalloping lesion at L4. **F**, T1-weighted image after gadolinium injection, lumbar level, sagittal view, better showing the epidural mass at L2 and the second epidural lesion at L4, strongly suggesting an enlarged venous pouch with bony scalloping. **G**, T2-weighted image, L2 level, axial view, showing an epidural mass in close relation with the L2 vertebral body. **H,** T1-weighted image after gadolinium injection at the L2 level.

Figure 2. Spinal angiography.

A, DSA, right L2 injection, posteroanterior projection, showing a SEAVF with rapid opacification of an isolated epidural venous pouch (arrows) principally draining retrogradely into the perimedullary venous system (arrowheads), without significant connection with the surrounding epidural plexus, black arrow points at the L2 ISA. **B**, DSA, right L2 injection, posteroanterior projection, post treatment (with NBCA glue), showing complete resolution of the SEAVF; the black arrow points at the L2 ISA. **C**, DSA, right L4 injection, posteroanterior projection documenting a SEAVF with rapid opacification of a large epidural venous pouch (asterisk) draining into an engorged epidural venous system, mostly on the left side (arrows). This SEAVF does not show retrograde perimedullary venous drainage. **D**, DSA, right L4 injection, posteroanterior projection post treatment (with detachable microcoils) showing complete resolution of the SEAVF. The black arrow points at the L4 ISA in both C and D.

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