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Concurrent multiple cerebral cavernous malformations and cauda equina paraganglioma: illustrative case

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BACKGROUND Cauda equina neuroendocrine tumors (CENETs), previously known as cauda equina paragangliomas, and multiple cerebral cavernous malformations (CCMs) are uncommon conditions affecting the central nervous system. To the authors' knowledge, they have not been reported in the same patient.

OBSERVATIONS The authors present the case of a 45-year-old male with CENET and concurrent incidental MRI findings of multiple CCMs. Familial CCMs are associated with mutations in the *KRIT1* (CCM1), *MGC4607* (CCM2), and *PDCD10* (CCM3) genes. Peripheral paragangliomas have been associated with mutations in succinate dehydrogenase (*SDHx*), *RET* (multiple endocrine neoplasia 2), *VHL* (von Hippel–Lindau syndrome), and *NF1* (neurofibromatosis type 1) genes. Except for a single case, cauda equina paragangliomas have not been associated with any underlying genetic mutations.

LESSONS It is unclear whether the co-occurrence of these two rare conditions in the same patient is coincidental or suggests a possible shared pathogenesis.

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KEYWORDS paraganglioma; cerebral cavernous malformation; cauda equina; neuroendocrine; tumor

Cerebral cavernous malformations (CCMs) are vascular malformations characterized by closely clustered dilated vascular spaces with hyalinized, fibrous walls lined by a single layer of attenuated endothelium, often without intervening brain parenchyma.[1] While cavernomas are mostly found in the brain, they have also been described in the spinal cord and other organs.[2] While the prevalence of CCMs is estimated to be around 0.5%, only 20%–30% of patients are symptomatic.[3] Common symptoms include headaches, seizures, and focal neurological deficits. Approximately 26% of patients may present with intracranial hemorrhage.[4]

Paragangliomas are rare neuroendocrine tumors arising from neural crest–derived cells in the paraganglia and adrenal medulla. They can occur in various sites, including the orbit, maxilla, larynx, thyroid gland, mediastinum, lung, para-aortic and retroperitoneal regions, spine, and adrenal medulla (pheochromocytoma). Histologically, they are composed primarily of chief cells arranged in nests ("Zellballen") and sustentacular cells.[5-7] The chief cells are immunoreactive for synaptophysin, chromogranin, and GATA3 and are negative for keratins, while the sustentacular cells express S100 and SOX10.[8]

Although cauda equina paragangliomas are morphologically identical to peripheral paragangliomas, they have several distinguishing features. They are typically hormonally silent (97% do not secrete catecholamines[9]) and are clinically indolent. They have a distinct methylome profile,[10] and they lack the genetic alterations characteristic of peripheral paragangliomas including mutations in *SDHx, VHL, NF1, HRAS*, and *MAML3* fusions.[10,11] Unlike peripheral tumors, they almost invariably express keratins and HOXB1 and do not stain for GATA3.[10-12] In the recently published fifth edition of the "WHO Classification of Endocrine and Neuroendocrine Tumours," cauda equina paraganglioma has been renamed cauda equina neuroendocrine tumor (CENET) to reflect these differences and is considered a distinct neuroendocrine tumor.[13]

While it is clear that there is a hereditary component that contributes to the development of both multiple CCMs and peripheral paragangliomas, no association between these two conditions has yet been described. We present a case of a 45-year-old male with a CENET and multiple CCMs.

ABBREVIATIONS CCM = cerebral cavernous malformation; CENET = cauda equina neuroendocrine tumor; MRI = magnetic resonance imaging.

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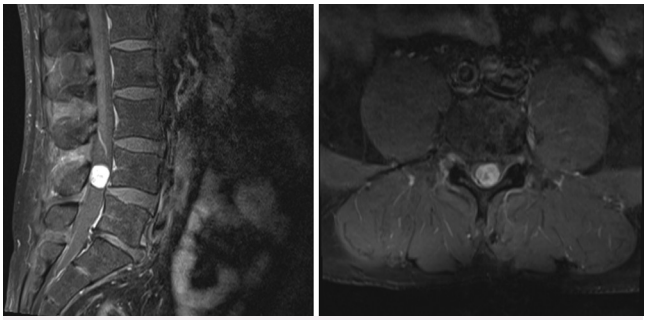

FIG. 1. Sagittal (**left**) and axial (**right**) postcontrast T1-weighted MRI scans demonstrating an avidly enhancing, well-circumscribed ovoid intradural extramedullary lesion in the cauda equina.

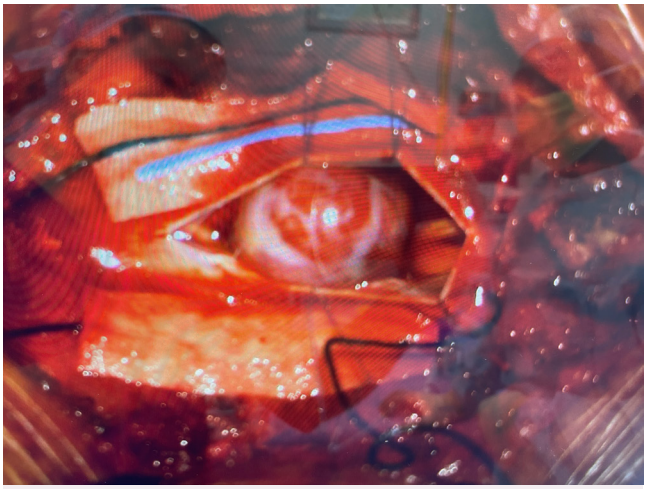

FIG. 2. Intraoperative photograph showing a well-circumscribed vascular encapsulated intradural tumor.

Illustrative Case

A 45-year-old male presented with 4 months of escalating pain involving the lower back, sacrococcygeal region, and pelvis with some radiation to the lower limbs. He did not report any weakness or changes in sensation. He had no sphincter disturbance. He had no other concurrent illnesses or history of previous medical conditions or surgeries.

His neurological examination was unremarkable. He had full range of motion in his lower limbs with full myotomal strength, present knee and ankle reflexes, and intact sensation including in the presacral region.

Lumbar spine magnetic resonance imaging (MRI) showed an intradural extramedullary lesion measuring 3 cm in the craniocaudal axis, involving and filling the entire L4–5 intervertebral space with compression of the lumbosacral nerves (Fig. 1). The lesion was rounded and well circumscribed and demonstrated homogeneous enhancement upon administration of gadolinium. There was complete effacement of cerebrospinal fluid. The differential diagnoses included nerve sheath tumor (i.e., schwannoma), myxopapillary ependymoma, and meningioma.

Given his significant pain and risk of neurological deficit and disability, the patient progressed to an L4–5 laminectomy and resection of intrathecal cauda equina tumor. Intraoperatively, we found a well-circumscribed vascular encapsulated tumor that was tethered cranially and caudally to the filum terminale via a single blood vessel (Fig. 2). This vessel was cauterized, and the tumor was dissected from its attachments craniocaudally and resected en bloc along with small arachnoid adhesions.

Pathological examination revealed an 18 × 15 × 13–mm, encapsulated tumor with microscopic features of a paraganglioma. The majority of the tumor cells (chief cells) were relatively uniform, round to polygonal with central round to ovoid nuclei and finely stippled chromatin. They were arranged in nests (Zellballen) bordered by a delicate capillary network resulting in an organoid pattern. Less conspicuous stellate and spindled sustentacular cells were also seen (Fig. 3). The chief cells were immunoreactive for synaptophysin, chromogranin A, and pancytokeratin. The sustentacular cells stained for S100 and SOX10 (Fig. 4).

Postoperatively, the patient recovered with no complications. Lumbar spine MRI 4 months postoperatively showed no evidence of recurrence. To screen for other lesions within the central nervous system, brain MRI was performed, and punctate foci of magnetic susceptibility in the right frontal pole, both parietal lobes, the left occipital lobe, and the right temporal lobe on the susceptibility-weighted imaging sequence were identified (Fig. 5). The differentials for these lesions included chronic microhemorrhages, foci of calcification, cerebral amyloid angiopathy, or CCMs. However, given the patient's age, multiple cerebral cavernomas were thought to be most likely.

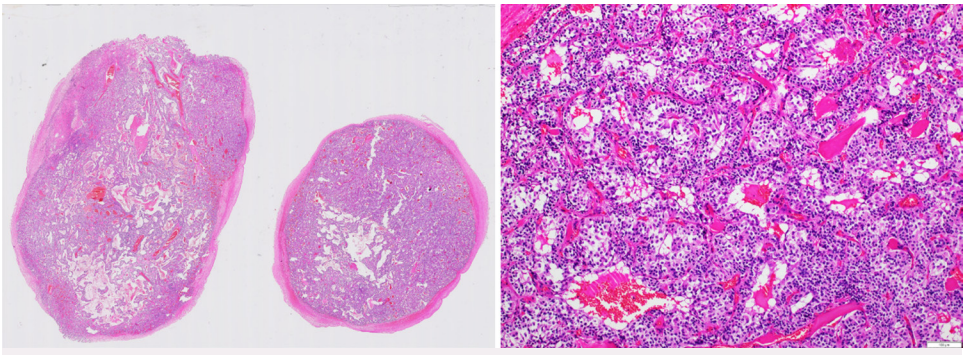

FIG. 3. Representative sections of the paraganglioma after hematoxalin and eosin staining. Original magnification unknown.

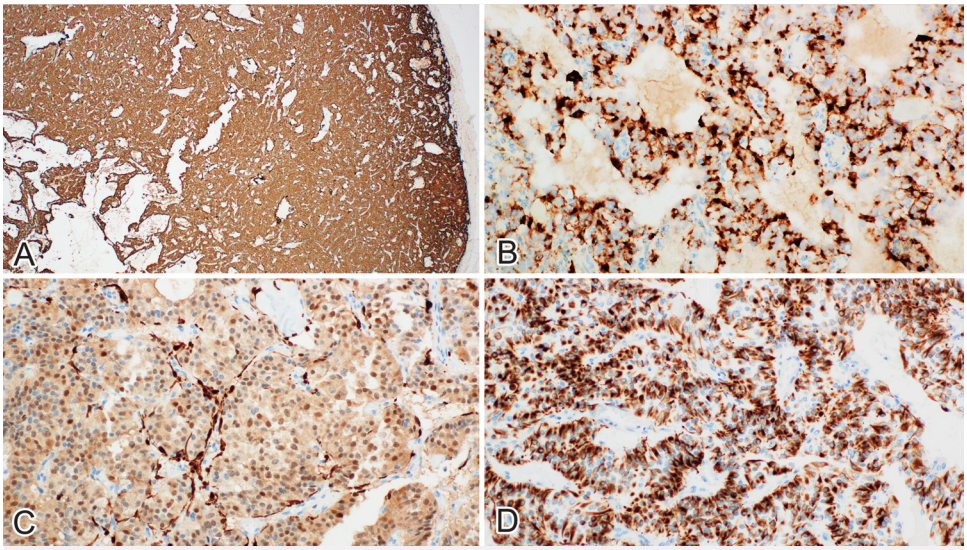

FIG. 4. Immunohistochemical staining with synaptophysin (**A**), chromogranin A (**B**), S100 (**C**), showing sustentacular cells, and pancytokeratin (**D**). Original magnification unknown.

No associated developmental venous anomalies were identified, and these lesions were incidental and asymptomatic. The patient did not report a known family history of cerebral cavernomas, although his immediate family members had not undergone radiological or genetic testing. The patient refused genetic counseling.

This illustrative case documents the previously undescribed co-occurrence of multiple CCMs and a CENET.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

CCMs can be divided into two subtypes, namely sporadic and familial. While most cases are sporadic, with only a single lesion, 10%–20% are familial.[14] Familial multiple cavernous malformation syndrome is defined as the presence of five or more CCMs; one CCM and at least one other family member with one or more CCMs; or a mutation in one of the three genes, associated with this disease (*KRIT1*, *CCM2*, or *PDCD10*).[15] The inheritance pattern is autosomal dominant with incomplete penetrance and variable expression.[16] Multiple lesions are more common in familial CCM, and the number of lesions strongly correlates with the patient's age with 0.2 to 0.4 new lesions appearing per patient-year.[17] In sporadic CCM, multiple lesions are uncommon (identified in approximately 10% of patients with sporadic CCM).[18,19] Although the pathogenesis of CCMs is not well understood, heterozygous loss of function mutations in three genes, *KRIT1* (CCM1), *MGC4607* (CCM2), and *PDCD10* (CCM3), are associated with familial multiple CCMs. Most mutations are nonsense, frameshift, and canonical splice-site mutations, although a minority

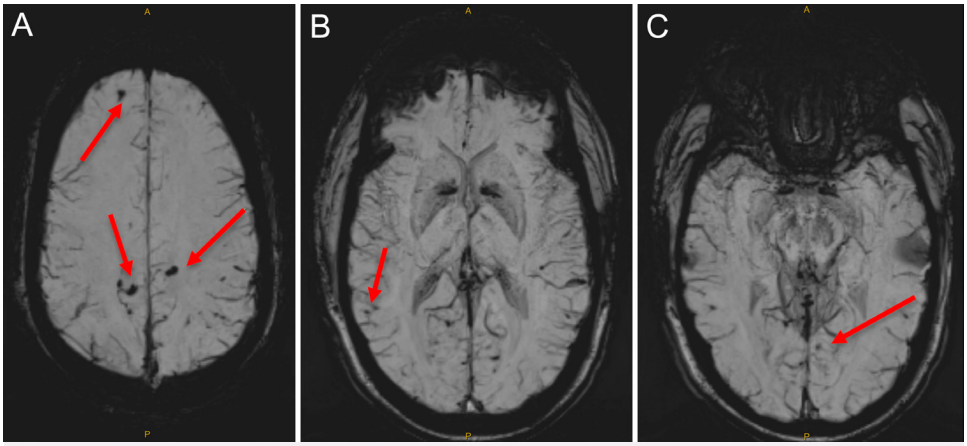

FIG. 5. Axial T2 susceptibility-weighted MRI sequences showing multiple punctate foci of magnetic susceptibility in the cerebral hemispheres, which represent CCMs. These are seen in the right frontal pole, both parietal lobes (**A**), the left occipital lobe (**C**), and the right temporal lobe (**B**).

are pathogenic missense mutations.[20] While mutations in these genes result in very similar phenotypes, the penetrance of each gene varies (*KRIT1*, 88%; *CCM2*, 100%; *PDCD10*, 63%)[21] and patients with *KRIT1* mutations may have cutaneous vascular lesions,[22] patients with *CCM2* mutations are more likely to be asymptomatic and have fewer cerebral cavernomas,[23] and patients with *PDCD10* mutation have a more aggressive clinical phenotype, with greater lesion burden and more frequent hemorrhages earlier in life.[24]

Similarly, paragangliomas can also be classified as sporadic or familial. While the majority of paragangliomas are sporadic, up to 30% of peripheral (non–cauda equina) tumors are familial.[9] About half of these are associated with germline mutations in succinate dehydrogenase (*SDH*) genes (*SDHB* or *SDHD*) and most show loss of *SDHB* expression.[10,25] Paragangliomas are also a component of several genetic tumor syndromes including multiple endocrine neoplasia 2, von Hippel–Lindau syndrome and neurofibromatosis type 1.[9,10] Despite this, cauda equina paragangliomas, existing as a separate tumor entity, are not associated with any other known abnormalities or syndromes. Additionally, despite the existence of familial peripheral paragangliomas, familial CENETs have not been described.[10,26,27] To date, there has only been one single case of a cauda equina paraganglioma with a germline mutation in *SDHD* which has been reported.[25] While CENETs share many morphological similarities with peripheral paragangliomas, they have a distinct clinical and immunohistochemical phenotype and methylation profile, hence earning themselves their new classification. Given the rarity of CENETs, with just over 200 cases reported in the English literature,[28-30] the cytogenesis, pathogenesis, and underlying genetic basis remain unclear.[26] With so few cases described, there are no reports to date of any syndromes or co-existing entities associated with CENETs.

There is currently no published literature regarding shared molecular or genetic findings between CCMs and CENETs, and to date there is no known common developmental or metabolic pathway. Although currently there is no supportive evidence, the possibility that there is a non-random association between these two rare conditions (multiple CCM and CENET) cannot be entirely excluded. By publishing this case report, we hope other authors will report similar cases, possibly leading to the identification of an underlying shared pathogenesis.

Limitations

The patient did not consent to genetic testing so germline CCM1–3 mutations could not be assessed. While the patient did not report a known family history of CCM, none of his immediate family members had undergone radiological or genetic assessment. As CCMs may be asymptomatic, it cannot be definitively concluded that the patient does not have a family history of familial CCM. Additionally, while the MRI findings are highly suggestive of cavernomas, other differentials including chronic microhemorrhages, calcifications, or cerebral amyloid angiopathy remain possible.

Although this patient did not consent to genetic testing, screening for known CCM genes would be appropriate. If additional cases with multiple CCMs and CENET are documented, further genetic testing such as trio whole exome/genome analysis could be considered in a research setting.

Lessons

Our case report describes a patient with a CENET and concurrent multiple CCMs. While the occurrence of two rare conditions in one individual may be the result of random association, it is possible that the two conditions share a common pathogenesis, possibly with a shared underlying genetic mutation. We encourage the reporting of further clinical associations between these two conditions. By accumulating more cases in the literature, a more compelling argument could be made for a thorough genetic analysis of both conditions, potentially leading to the discovery of a unifying genetic mechanism.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Liu, Ghahreman. Acquisition of data: Liu, Rodriguez, Ghahreman. Analysis and interpretation of data: Rodriguez. Drafting the article: Liu. Critically revising the article: Rodriguez, Ross, Ghahreman. Reviewed submitted version of manuscript: Liu, Rodriguez, Ghahreman. Approved the final version of the manuscript on behalf of all authors: Liu. Administrative/technical/material support: Ghahreman. Study supervision: Ghahreman.

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