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Vertebral Intraosseous Vascular Malformations in a Familial Cerebral Cavernous Malformation Population: Prevalence, Histologic Features, and Associations With CNS Disease

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Abstract

OBJECTIVE.—The purpose of this study was to investigate whether MRI-typical and MRI-atypical intraosseous vascular malformations are associated with familial cerebral cavernous malformation (FCCM).

MATERIALS AND METHODS.—In a retrospective matched case-control study, two radiologists reviewed the spinal imaging, both CT and MRI, of 22 patients with FCCM seen between 2006 and 2017 and of age- and sex-matched control subjects for MRI-typical and MRI-atypical intraosseous vascular malformations. Quantitative analysis of lesions identified included vertebral level, size, and number of lesions. Pathologic samples from two lesions were analyzed for histologic and immunohistochemical features. Whether the presence of typical, atypical, and total intraosseous vascular malformations differed between patients and control subjects was tested. For patients with complete spinal imaging, whether intraosseous vascular malformations were associated with age, sex, brain lesion count, and spinal lesion count was also tested.

RESULTS.—MRI-atypical intraosseous vertebral malformations were more commonly present in patients with FCCM ($p = 0.003$). Sixteen lesions were found in nine patients and none in the control group. The numbers of MRI-typical intraosseous vascular malformations were similar between patients and control subjects ($p = 0.480$). Age was associated with typical intraosseous vascular malformations ($p = 0.027$), though not with atypical malformations. MRI-atypical malformations were larger (mean diameter double) than MRI-typical malformations ($p = 0.023$). Histologic analysis of two lesions from different patients with pathologic collapse revealed the same histologic features consistent with combined capillary-venous malformations.

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CONCLUSION.—Vertebral capillary-venous malformations (MRI-atypical intraosseous vascular malformations) are common in patients with FCCM and may have a more aggressive clinical course than MRI-typical malformations.

Keywords

cerebral cavernous malformation; intraosseous vascular malformation; neurocutaneous disorder; spinal cavernous malformation; vertebral hemangioma

Familial cerebral cavernous malformation (FCCM) is an autosomal dominant genetic disorder that carries the risk of serious clinical outcomes. This disorder, which is characterized primarily by formation and growth of cavernous malformations within the brain and spinal cord, is recognized as a multisystem neurocutaneous disorder. Vascular lesions can be found in the retina, adrenal glands, and skin of patients with FCCM [1-4]. Scattered reports exist of intraosseous vascular malformations, commonly referred to as vertebral hemangiomas, in these patients, with a presumed shared cause of the intraosseous and CNS lesions. However, intraosseous vascular malformations are prevalent in the general population and are generally of limited clinical significance. Previous anecdotal reports of intraosseous vascular malformations in association with CCM disease have not taken into account this background prevalence of intraosseous vascular malformations.

Intraosseous vascular malformations are the most common vascular lesions in bone [5, 6]. They are composed of a lattice of vascular spaces that displace bone and cause reactive new bone formation with thickened trabeculae. The interstitium of the lesions is composed of adipocytes, bone, smooth muscle, and edema. A few case reports exist of intraosseous vascular malformations in patients with FCCM [7, 8]. One report described eight members of an Italian family with FCCM, three of whom had intraosseous vascular malformations [9].

Assessment of reports of CCM is to some degree limited by the fact that, as radiologists and spinal clinicians are aware, intraosseous vascular malformations are common findings at routine CT and MRI of adults. An autopsy study [5] showed that intraosseous vascular malformations were present in 11% of bodies examined, and later CT and MRI studies of large numbers of adults showed the malformations present in approximately 26% of subjects [10, 11]. Intraosseous vascular malformations are known to have an increasing prevalence with age [10]. Most are clinically unimportant, although unusually large or fat-poor malformations are at greater risk of pathologic fracture [12-14]. In the setting of the high prevalence of these malformations in the general population, the clinical significance of intraosseous vascular malformations in patients with FCCM was less clear and led us to investigate a potential association in more detail.

We evaluated a cohort of patients with a shared *CCM1* mutation and compared characteristics of intraosseous vascular malformations in the patient cohort with those in a matched control group. We hypothesized that intraosseous vascular malformations are more common in the population with FCCM. We also looked for correlations between the presence of intraosseous vascular malformations and brain and spinal cavernous malformations in the FCCM group and correlated MRI and pathology findings in two

surgical cases. These revealed pathologically and radiologically distinct intraosseous vascular malformations in the bone marrow of patients with FCCM.

Materials and Methods

This HIPAA-compliant retrospective case-control study received institutional review board approval. The requirement for informed consent was waived for this retrospective study. There were no financial conflicts of interest.

Patients

A medical record search was conducted on cross-sectional spinal imaging of patients known to have FCCM type 1 (FCCM1) because of their enrollment in a National Institutes of Health–funded prospective study. The search identified 21 patients with FCCM and two other patients with CCM, family history, and Hispanic ethnicity [15]. All patients had FCCM confirmed by genetic testing, brain imaging, or both.

Twenty of the 23 patients identified had undergone MRI of the spine, and two had undergone only CT. One patient who had undergone spinal MRI was excluded for having metastatic breast cancer. A total of 45 MRI and two CT studies of the spine of these patients with FCCM were reviewed. Only the MRI data were used for statistical analysis. The 21 patients enrolled in the prospective study had either positive genetic testing results confirming the *CCM1* common Hispanic mutation (CHM) or multiple CCM brain lesions and a known first-degree relative with positive genetic testing results for *CCM1*-CHM. The 21 patients had undergone genetic testing for *CCM1*-CHM. All 23 patients identified in the current study had undergone brain MRI, including imaging of part or all of the spine.

Control subjects without FCCM were matched to patients with FCCM1 for sex, age (within 2 years for adults and 1 year for children), and Hispanic ethnicity. Control subjects were confirmed not to be carriers of FCCM by either negative gene testing results or brain MRI negative for CCMs. All control subjects had undergone spinal MRI matched by segment of the spine imaged (cervical, thoracic, lumbar) corresponding to the matched subjects with FCCM. Control subjects were identified by search of the PACS for the first patient matching each study subject for corresponding age, sex, ethnicity, and spinal imaging study who had also had undergone prior MRI of the brain that showed no evidence of CCM. Spinal imaging findings were not reviewed until after control subjects were selected.

Imaging

We retrospectively evaluated spinal images for intraosseous vascular malformations. Malformations with atypical features varied from those with typical features in that they were hyperintense on T2-weighted images but hypointense on T1-weighted images. Lesions were classified on the basis of location, size, appearance, multiplicity, and interval changes in patients who had undergone serial studies. Two board-certified fellowship-trained radiologists—a neuroradiologist and a musculoskeletal radiologist—reviewed the imaging independently before arriving at a consensus interpretation of the lesions. We excluded lesions with indeterminate imaging features, metastases, and other, nonintraosseous vascular malformations. Patients enrolled in the prospective study previously had brain lesions

counted on gradient-recalled echo MR images. Brain and spinal imaging of the patients with FCCM1 and control subjects was performed between 2006 and 2017, and all spinal imaging was performed at the parent institution (University of New Mexico). MRI was performed at 1.5 or 3 T and included fast spinecho T1- and T2-weighted sequences.

Pathologic Analysis

Fresh surgical specimens from two patients with FCCM who had pathologic fractures and underwent resection were sent to the pathology department, fixed in 10% neutral buffered formalin, placed in ethylenediaminetetraacetic acid for decalcification, and embedded in paraffin according to standard clinical histologic procedures at the parent institution. Sections were cut at 5 μ m, stained with H and E, and covered with a coverslip. Representative blocks of lesions were cut into 5- μ m-thick sections, mounted on charged slides, deparaffinized, and individually stained by the immunoperoxidase method with antibodies to CD34 (endothelial marker), CD31 (endothelial marker), D2-40 (primarily a lymphatic channel marker), smooth-muscle actin (SMA) (expressed in actin-rich cells, including pericytes and muscle cells in vessel walls), and Ki67 (expressed in cells actively proceeding through the cell cycle; e.g., negative in the G₀ phase). All antibodies and the Vantage automated immunohistochemical Stainer were obtained from Ventana Medical Systems. Slide processing included pretreatment specific to each antibody. Diaminobenzidine served as the chromogen. Positive and negative results in control subjects confirmed staining specificity.

Statistical Analysis

We calculated summary statistics and performed statistical analyses using patient-level, image-level, and intraosseous vascular malformation-level data. For patient-level data, we used the Wilcoxon signed rank test to test whether the prevalence of typical and atypical intraosseous vascular malformations differed between the 20 patients with FCCM and the matched control subjects. For scan-level data, we used the Fisher exact test to determine whether typical or atypical intraosseous vascular malformations were associated with a particular spinal region.

We used ordered logistic regression (assessing a single predictor at a time) to test whether the number of typical or atypical intraosseous vascular malformations was predicted by age, sex, brain lesion count, or spinal cord lesion count. Brain lesion counts were log-transformed (base 2) before analysis to accommodate outlier values. These regression models included indicator variables to account for scan region (i.e., cervical, lumbar, and thoracic), and standard error was adjusted to accommodate for patient-level effects. Results of these regression models were reported as odds ratio (OR) with 95% CI

For intraosseous vascular malformations-level data, we used a two-sample *t* test allowing unequal variances to test whether the maximal diameter between typical and atypical intraosseous vascular malformations differed in patients with FCCM. We treated intraosseous vascular malformations as independent observations because there was no evidence of a patient-level effect on maximal diameter in a mixed-effects linear regression

model ($p = 1.000$). We tested whether the maximal diameter of typical intraosseous vascular malformations differed between patients with FCCM and control subjects.

Statistical analyses were performed with Stata software (version 15.1, StataCorp). We considered $p < 0.05$ to be statistically significant.

Results

Imaging

The mean age of the 20 patients with FCCM1 was 41 years (range, 3–73 years), and that of the 20 control subjects was 40 years (range, 3–72 years). There were six male and 14 female subjects in each group. The cervical region was assessed in 19 (95%) subjects in each group, the thoracic region in 15 (75%), and the lumbar region in 11 (55%). All subjects self-reported Hispanic ethnicity. Brain lesion count was available for 16 patients with FCCM1; the median brain lesion count was 19 (range, 1–418 lesions). Spinal lesion count was available for 18 patients with FCCM1; the median value was 1 lesion (range, 0–11 lesions). The indications for imaging in the FCCM1 group were neurologic signs and symptoms ($n = 14$ [70%]) and back or neck pain ($n = 9$ [45%]); these indications are not mutually exclusive.

Intraosseous vascular malformations with an MRI-typical appearance (hyperintense on both T1- and T2-weighted images) were found in six patients with FCCM1 and five control subjects, who had seven and five, respectively, total typical malformations counted (Table 1). The groups did not differ statistically with regard to MRI-typical malformations ($p = 0.480$). MRI-atypical malformations were present in nine (45%) of the patients with FCCM1 and in none of the control subjects ($p = 0.003$) (Figs. 1 and 2). We observed 16 atypical malformations in total, as many as three in a single patient.

Correlative evidence for intraosseous vascular malformations varied. Pathologic examination results were available for two subjects. One did and the other did not have MRI studies available to us. For five patients with 11 lesions, both MRI and CT showed findings consistent with intraosseous vascular malformations (nonaggressive features with stippled or corduroy appearance). Most underwent repeat, stable imaging over a period of years. One subject also underwent a PET study that did not show abnormal FDG uptake to indicate an aggressive neoplasm, and one had histologic confirmation. Four subjects with five lesions did not have CT correlation but had a benign clinical course without evidence of neoplasm for 2, 6, 7, and 12 years. The patients with 2- and 6-year follow-up also had repeat stable MRI findings. Further details are shown in Table 2. As a more conservative evaluation, the comparison between FCCM and control groups remained statistically significant even when the lesions in patients with only long-term clinical follow-up were excluded ($p = 0.009$) or lesions in patients with only clinical or MRI evidence were excluded ($p = 0.026$).

One of the two patients who underwent CT only was a 60-year-old man who had a presumed intraosseous vascular malformation measuring $3.1 \times 2.7 \times 2.6$ cm in the L2 vertebral body. The posterior margin of the vertebral body was deformed by the lesion, slightly narrowing the spinal canal. Attenuation within the lesion was 49.0 HU (SD, 20.8 HU) in an ROI within the center of the lesion. No low-attenuation fatty regions were identified, consistent with a

fat-poor atypical intraosseous vascular malformation. The other patient, a 44-year-old woman, had CT images of the cervical spine that did not show an intraosseous vascular malformation. This patient had undergone T12 vertebrectomy 15 years previously because of cauda equina syndrome. Imaging from that time was not available, but the histologic results were (see Histologic and Immunohistochemical Features). Control subjects who had corresponding CT scans had no findings to suggest intraosseous vascular malformations. The patients who underwent only CT were not included in the quantitative analysis to keep the patients being compared as similar as possible.

Among the patients with FCCM, we found typical intraosseous vascular malformations more frequently in the thoracic region (40%) than the lumbar region (9%) or cervical region (0%) ($p = 0.004$). Atypical intraosseous vascular malformations tended to be more evenly distributed across the three regions ($p = 0.902$). In regression analysis, we found that each decade increase in age was associated with the presence of typical intraosseous vascular malformations in patients (OR, 1.59; 95% CI, 1.05–2.40; $p = 0.027$). Each doubling of lesion count was also associated with the presence of typical malformations (OR, 1.76; 95% CI, 1.04–2.98; $p = 0.034$). Spinal cord lesions were not significantly associated with typical malformations but exhibited a large effect size (OR, 2.17; 95% CI, 0.99–4.74; $p = 0.053$). Patient sex was not associated with typical intraosseous vascular malformations ($p = 0.274$).

With respect to the outcomes of atypical intraosseous vascular malformations, we found large, but nonsignificant, effects for each decade increase in age (OR, 1.42; 95% CI, 0.92–2.20; $p = 0.116$) and each doubling of the number of brain lesions (OR, 1.26; 95% CI, 0.98–1.61; $p = 0.068$). Spinal cord lesions ($p = 0.474$) and patient sex ($p = 0.698$) were not associated with the presence of atypical intraosseous vascular malformations. Atypical malformations tended to be larger on average than typical malformations (1.78 vs 0.87 cm; $p = 0.023$). The largest atypical malformation was 5.6 cm, compared with a maximal diameter of 1.2 cm among typical intraosseous vascular malformations.

Typical intraosseous vascular malformations in patients with FCCM did not differ in size compared with those in control subjects (0.87 vs 0.88 cm; $p = 0.968$). In one patient with an MRI-atypical malformation, a lesion had grown from 0.5 to 1.4 cm in diameter between studies 17 months apart (Fig. 3).

Some information was available regarding other findings of FCCM disease (Table 2). Six of the 17 patients had skin lesions considered by a dermatologist to be vascular malformations related to FCCM. One of these patients also had multiple vascular lesions seen on MRI studies of the forearm. Eight patients previously underwent CT for clinical reasons that covered the adrenal glands; five of the eight had small adrenal calcifications.

Histologic and Immunohistochemical Features

Two of the patients in the FCCM group had pathologic collapse of a thoracic vertebral body (Fig. 4) and underwent corpectomy and instrumentation and histologic analysis of the lesion. Both lesions comprised a disorderly mix of thin and thick-walled, small- to medium-sized blood vessels embedded in a fibrous to focally myxoid stroma. The stroma and vessels entirely replaced marrow fat and hematopoietic elements (Fig. 4C). Residual bone

trabeculae were encased in some areas and effaced in other areas. Some bone trabeculae exhibited reactive thickening and distorted shapes consistent with reactive immature bone. Lesional vessels were variably ectatic, and some were markedly dilated (cavernous). A muscular wall was detected with H and E staining in the thicker-walled venous component. Other vessels appeared to consist of only a single attenuated layer of endothelium. One lesion had evidence of prior vessel damage with Masson hemangioma change. However, recent thrombi comprising layers of fibrin were not identified in either case. Vessel damage could have occurred from microfracture or vertebral body collapse and may not have arisen as a de novo event. Hemosiderin deposition was rare, comprising a few foci of one to three pigment-laden histiocytes in the stroma. Histologically significant inflammation, including mast cells, was absent.

Both lesions had identical immunohistochemical results. The endothelial lining cells diffusely strongly expressed CD34 and CD31 with no expression of podoplanin (D2-40). SMA expression was present in all thicker vessels and in approximately 90% of the thin-walled ectatic vessels. In the latter, the SMA exhibited a delicate, thin, single-cell-wide band of reactivity (Fig 5). Some vessels exhibited discontinuous SMA reactivity (some of the thin-walled vessels) or irregular thick and thin reactivity (some of the thicker-walled vessels). Only rare cells expressed Ki67 for overall approximately 1% percent reactivity. However, areas of increased reactivity were present with nuclear expression in both endothelial cells and scattered stromal cells regionally in as many as 10% of cells (Fig. 4D). Table 3 shows the antibodies used and the results.

Discussion

FCCM disease is a complex, multisystem disorder. Cavernous malformations in the brain are usually multiple, sometimes numbering in the hundreds. Vascular lesions in the retina in approximately 5% and in the skin in 20% of patients have also been reported [1-3], as have small adrenal calcifications [4]. The question of skeletal involvement is complicated by the common occurrence of intraosseous vascular malformations, commonly referred to as vertebral hemangiomas, in the general population, prompting us to include a matched control group. The FCCM group differed markedly from the control group—not with respect to MRI-typical but regarding MRI-atypical intraosseous vascular malformations. In comparison with a control group matched for age, sex, and ethnicity, the patients with *CCMI*-CHM had similar prevalence and size of MRI-typical malformations but had an unexpectedly high prevalence of MRI-atypical malformations whereas the control group had none.

Although MRI-atypical intraosseous vascular malformations are certainly seen occasionally in clinical practice and are not limited to FCCM, our results are far different from those in the general population. More MRI-atypical than MRI-typical malformations were observed in the FCCM population, they were often multiple, and they were larger than in the control subjects. We conclude that patients with FCCMs have a similar prevalence of MRI-typical intraosseous vascular malformations as the general population but that FCCM status is associated with fat-poor, MRI-atypical lesions.

The basic histologic features of MRI-atypical intraosseous vascular malformations in two patients were identical and consistent with a combined capillary-venous malformation described in the 2014 International Society for the Study of Vascular Anomalies classification [16]. Lesions are designated capillary-venous malformations because of the dual presence of vessels formed by a single cell layer (capillaries) and thick-walled vessels with a definite muscular wall (veins). No lymphatic component was identified. Both lesions exhibited complete replacement of marrow fat with retention of at least some intermixed residual bone trabeculae. Some of the residual bone trabeculae exhibited woven bone deposition consistent with a reactive response. These histologic findings correspond to the MRI results of low signal intensity on T1-weighted images and absence of regions of fat on CT images.

The lack of a lymphatic component in the two patients is consistent with intraosseous vascular malformations arising in patients with FCCM, because the characteristic intracerebral cavernous malformation also lacks a lymphatic channel component [17]. In both cases, thin-walled (cavernous) channels exhibited SMA reactivity albeit at the width of a single cell. However, the walls of some of the larger vessels were also remarkable for irregular thin and thick bands of SMA reactivity suggesting abnormal dysplastic (in the nonpreneoplastic sense of the term) development of smooth-muscle cells.

A second unusual finding in both cases is the evidence of ongoing proliferative capacity as detected by rare but extant Ki67 reactivity, including a few endothelial cells but also scattered stromal cells. Although the overall percentage reactivity was only approximately 1%, foci of up to 10% reactivity were present. This finding suggests that these lesions continue to proliferate, if slowly. There is sparse information on Ki67 reactivity in vascular malformations [18, 19]. Possibly, in patients with FCCM specifically, the growth of current lesions and development of new lesions in the vertebrae may be ascribable in part to low ongoing proliferative capacity.

Intraosseous vascular malformations may have more aggressive and clinically meaningful features, as found in the two patients in the study group who had a pathologic fracture with spinal cord compression, by the lesion that underwent remodeling and thinning of the posterior vertebral cortex, and by another with fairly rapid growth. It is also important because neoplasia, especially metastasis, is frequently a diagnostic dilemma with T1-hypointense–T2-hyperintense marrow lesions. Although a neoplasm can coexist with FCCM, the radiologist should be aware of the common occurrence of capillary-venous malformations in FCCM.

Our study had several limitations, including retrospective design and moderate number of patients with CCM with available spinal MR images and CT scans. However, the inclusion of matched control subjects revealed a significance difference despite the sample size. Areas of focal fatty deposition may be difficult to differentiate from intraosseous vascular malformations [20], but we expect that this would affect both groups to a similar extent. The imaging was interpreted without blinding to clinical diagnosis of FCCM, a potential source of bias. Another limitation for broader applicability to all patients with CCM was that our population of patients with FCCM is composed almost entirely of *CCMI*-CHM carriers.

Variant *CCM1* mutation, *CCM2*, or *CCM3* carriers may have different expression. Sporadic patients with CCM lack germline mutations and are unlikely to have systemic manifestations. Having pathologic results from only two lesions was also a limitation, and further sampling would increase certainty and power. The additional, supportive evidence for the presumed diagnosis of intraosseous vascular malformation for the T1-hypointense–T2-hyperintense lesions does vary, although this is unlikely to affect the overall conclusions.

Conclusion

Although FCCM disorder is characterized primarily by the presence of CNS lesions, this study and others show a clearer picture of the systemic nature of the disorder. FCCM is associated with vertebral lesions, broadly diagnosed as atypical intraosseous vascular malformations but more precisely characterized histologically as combined capillary-venous malformations, which may have more aggressive pathologic and clinical presentations.

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Fig. 1—

51-year-old woman with proven familial cerebral cavernous malformation (FCCM), back pain, and neurologic signs and symptoms. Example of multiple MRI-atypical intraosseous vascular malformations in single patient with FCCM.

A, T1-weighted MR image shows area of low signal intensity filling much of L3 vertebral body and well-demarcated round areas within L2 and T1.

B, Sagittal CT reconstruction shows coarse, vertical trabeculations (corduroy pattern) of L3 lesion. L2 lesion is not clearly visible in this slice.

C and **D**, Sagittal T1-weighted (**C**) and T2-weighted (**D**) MR images show T1 lesion has low T1 signal intensity and T2 prolongation. Lesions were stable at 10-year follow-up MRI.

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Fig. 2—.

57-year-old man with proven familial cerebral cavernous malformation and right-sided weakness.

A, Sagittal STIR MR image shows high-signal-intensity lesion within marrow space of C4 vertebral body, cavernous malformation in brainstem, and small cavernous malformation (*arrow*) on dorsal surface of spinal cord at C4.

B, Sagittal CT reconstruction shows corduroy pattern of thickened vertical trabeculation with intervening low attenuation (*arrow*).

C, Axial T2-weighted multiecho data image combination MRI image at C4 shows high-signal-intensity lesion in vertebral body and two spinal cord cavernous malformations (*arrows*).

D, Axial T1-weighted MR image shows low signal intensity of atypical intraosseous vascular malformation. MRI appearance of osseous lesion was stable over 2 years.

Fig. 3—.

55-year-old man with familial cerebral cavernous malformations. Example of growth of MRI-atypical intraosseous vascular malformations.

A, Initial sagittal T1-weighted MR image shows typical intraosseous vascular malformation within L4 as very small focus (*arrow*) of low signal intensity.

B, Initial axial T2-weighted MR image shows typical intraosseous vascular malformation in L2 as very small focus (*arrow*) of high signal intensity.

C and **D**, Sagittal (**C**) and axial (**D**) MR images 17 months after **A** and **B** show growth to 1.4 cm with coarse stippled appearance (*arrow*).

Fig. 4—.

40-year-old woman with sudden, severe back pain due to pathologic fracture.

A, Sagittal T1-weighted MR image shows replacement of normal T12 marrow and collapse with spinal cord compression. Small, typical T1-hyperintense lesion is present in T9. Patient underwent T12 corpectomy and instrumentation.

B and **C**, Photomicrographs (**B**, H and E, medium magnification; **C**, Ki67 antibody stain, high magnification) show anastomosing blood vessels embedded in fibrous stroma replacing marrow fat. Ki67 is expressed in scattered endothelial nuclei (*yellow arrow*, **C**) and stromal cell nuclei (*blue arrow*, **C**) consistent with low proliferative capacity.

Fig. 5—
44-year-old woman with familial cerebral cavernous malformations and pathologic fracture managed surgically.
A, Photomicrograph (smooth-muscle actin [SMA] antibody stain, medium magnification) shows expression of SMA even in thin-walled vascular channels.
B, Axial T2-weighted gradient-recalled echo MR image shows multiple cerebral cavernous malformations in brain.

TABLE 1:
Number and Size of Intraosseous Vascular Malformations in Study and Control Groups

Characteristic	Group With Familial Cerebral Cavernous Malformations	Control Group
No. of intraosseous vascular malformations		
MRI atypical	16	0
MRI typical	7	5
Mean maximum diameter of intraosseous vascular malformations (cm)		
MRI atypical	1.85	NA
MRI typical	0.87	0.88

Note—NA = not applicable.

TABLE 2:
Lesion Information for Patients With Familial Cerebral Cavernous Malformations (FCCMs) and Control Subjects

Subject No.	Sex	Indication for Spinal Imaging	Age at Spinal Imaging (y)	Patients With FCCMs										Control Subjects ^a					
				Typical Intraosseous Vascular Malformations			Atypical Intraosseous Vascular Malformations			No. of Brain CMs at Baseline	No. of Spinal CMs	Adrenal ^c	Skin Lesions	Age at Spinal Imaging (y)	Typical Intraosseous Vascular Malformations				
No.	Modality	Size (mm)	Level	No.	Evidence ^b	Size (mm)	Level	Yes	No						U	No	No.	Level	Size (mm)
1	F	Neurologic symptoms; back pain	73	MRI C, T, L	1	10	T1	0				96	3	Yes	No	72	1	T9	10
2	M	Neurologic symptoms	17	MRI C, T, L	0			0				9	1	U	Yes	17	1	T9	7
3	M	Neurologic symptoms; back pain	30, 30, 34	MRI C, T, L	1	5	T5	0				22	1	U	No	34, 28, 28	0		
4	M	Neurologic symptoms	5	MRI C, T, L	0			0				2	1	No	Yes	5	0		
5	F	Back pain	65	MRI C, T	0			0				185	1	No	No	65	0		
6	F	Neurologic symptoms	34	MRI C, T	1	10	T3	1	MRI (7 y)	27	T11	31	2	U	No	32	0		
7	F	Neurologic symptoms	43	MRI C, T, L	0			1	MRI (12 y)	11	L3	194	3	U	Yes	41	0		
8	F	Neurologic symptoms	64	MRI C, L	0			0				88 (clinical, 1.5 T, SWI)	2	U	No	63	1	T8	7
9	M	Neurologic symptoms	57	MRI C, T, L	2	7, 12	T11, L4	2	CT, CT	6, 16	L1, L2	418	11 ^d	U	No	55	1	L2	15
10	F	Neurologic symptoms	41	MRI C	0			0				118	2	U	No	41	0		
11	F	Back pain	21	MRI C	0			0				10	2	U	Yes + MRI	22	0		
12	F	Neurologic symptoms	32	MRI C, T, L	0			0				3	1	U	U	34	1	T11	5
13	F	Back pain	46	MRI C, T	0			1	MRI (6 y, repeat MRI)	20	L1	46	2	U	No	47	0		
14	F	Injury	44	CTC	0			0	H			51	1	No	Yes	44	0		

Subject No.	Sex	Indication for Spinal Imaging	Age at Spinal Imaging (y)	Patients With FCCMs						Control Subjects ^d			
				Typical Intraosseous Vascular Malformations			Atypical Intraosseous Vascular Malformations			No. of Brain CMs at Baseline		No. of Spinal CMs	
				Modality	No.	Size (mm)	Level	No.	Evidence ^b	Size (mm)	Level	Adrenal ^c	Skin Lesions
15	F	Neurologic symptoms	21	MRI C, T	0			0				1	No
16	F	Neurologic symptoms	51	MRI C	0			2	MRI, MRI (2 y, repeat MRI)	10	C5, T1	1	Yes
17	F	Neurologic symptoms; back pain	51, 53	MRI C, L	0			3	CT	12, 22, 41	T1, L2, L3	0	U
18	M	Gastrostomy tube placement	60	CT abdomen	0			1		31	L2	NA	No
19	F	Back pain	3	MRI C, T, L	0			0				0	No
20	M	Back pain	60	MRI T	1	5	T7	2	CT, CT (also normal PET)	10, 8	T3, T11	1	U
21	M	Neurologic symptoms	57	MRI C, T	0			1	CT (repeat MRI)	16	C4	6	U
22	F	Back pain; T12 fracture	40	MRI C	1	12	T9	3	CT, H, CT	5, 56, 5	C6, T12, T7	0	U

Note—CMs = cavernous malformations, C = cervical spine, T = thoracic spine, L = lumbar spine, U = unknown (no CT studies available to assess), SWI = susceptibility-weighted imaging, NA = not applicable (only CT), T2GRE = T2-weighted gradient-recalled echo.

^aNo control subject had atypical intraosseous vascular malformations.

^bMRI = only MRI available but with multiyear clinical information, CT = CT correlation, H = histologic evidence (surgery).

^cSmall adrenal calcifications.

^dTwo of these spine lesions were in nerve roots; the rest were intramedullary.

TABLE 3:

Antibodies Used and Immunohistochemical Staining Results in Two Cases of Intravertebral Combined Capillary-Venous Malformations

Antibody	Result	Primary Antibody Clone	Species
CD34	100% reactivity in specific cell of interest	QBend/10	Mouse
CD31	100% reactivity in specific cell of interest	JC70	Mouse
Podoplanin	0% reactivity	D2-40	Mouse
Smooth-muscle actin	Up to 90% reactivity (90% of thin-walled vessels and 100% of thick-walled vessels with irregular deposition in thick-walled vessels and some discontinuous reactivity in thin-walled vessels)	1A4	Mouse
Ki67	Up to 10% reactivity (1% focally up to 10%)	30-9	Rabbit

Note—All antibodies were obtained from Ventana Medical Systems.