Intracerebral cavernous malformations (ICMs) are angiographically occult vascular malformations with a characteristic radiographic and pathological appearance. The natural history of these lesions has been reported in numerous series; however, these studies have typically grouped all patients together—that is, those with incidental findings of ICM and those who are symptomatic—to define overall hemorrhage rates. It is more clinically useful to provide patients with hemorrhage rates and natural history data that pertain to their situation and initial presentation. Previous studies have been further limited by the duration of follow-up, typically limited to a mean of 2–5 years.

The incidental detection of ICMs, whose estimated prevalence is between 0.15% and 0.6% in the general population, may be increasing, probably because of the increased availability and utilization of brain MRI. Approximately 20%–50% of clinical series include patients with no symptoms, and in whom the ICM is an incidental finding.

Given the prevalence of this disorder and the need for longer-term hemorrhage rates, we aimed to determine the prospective hemorrhage rate in a group of retrospectively identified patients in whom symptoms had an unclear relationship to an intracerebral cavernous malformation (ICM) or the malformation itself was an incidental finding.
Hemorrhage rate in incidental cavernous malformations

Incidental finding. We also aimed to determine the incidence of new seizures in these patients.

Methods

Patient Selection

Patients in this study, those with an incidentally found ICM or those in whom the ICM had an unclear relationship with existing symptoms, were identified from a prior cohort. This dataset consisted of patients with CMs entered into a radiology database between 1989 and 1999 at the Mayo Clinic in Rochester, Minnesota. The original dataset comprised 329 patients with CMs or angiographically occult vascular malformations. A subsequent review by the primary investigator (K.D.F.) yielded 292 well-defined patients with CMs based on radiographic criteria. Of this group, 74 patients had sustained rupture of the CM and were described in our original publication, and 108 had no symptoms related to the CM. The remaining 110 patients had a CM that was an incidental finding or had an unclear relationship to the presenting symptoms, and this group is the subject of the current study.

Data Collection

The follow-up clinical records of patients from this dataset were reviewed between 2011 and 2012. If patients had been seen at our institution within 6 months of our review, we used clinical and radiographic information from the medical record to determine new neurological events, and the patient was not directly contacted. If patients had not been recently seen at our institution, a mail survey was sent, followed up by a phone call. If patients did not return a paper survey, phone calls were made. Imaging studies obtained elsewhere were requested if there was concern about a new neurological event. If no data could be obtained, the last follow-up data obtained for the patient was used (from the 2003 epoch). Attempts were made to obtain data on patients who died in the 2011–2012 time frame. If a patient was deceased, death records were obtained when possible. In some cases, relatives of deceased patients were contacted, and outside data, including imaging studies, were obtained. When data were not available, it was assumed that the patient did not experience a clinically significant hemorrhage.

Recorded follow-up information also included surgery or radiosurgery since diagnosis and whether symptomatic hemorrhage or seizure due to the ICM had occurred. A “definitive prospective hemorrhage” was defined as a new clinical event (focal deficit, seizure, or severe headache) in association with radiographic evidence of acute hemorrhage or autopsy data suggesting acute hemorrhage. A “probable prospective hemorrhage” was defined as a clinical event suggesting intracerebral hemorrhage according to records from a medical institution outside our medical record system, but no imaging studies to personally review. An “undocumented prospective hemorrhage” was defined as an acute clinical event, but no imaging report or imaging studies to personally review. The definition of definitive hemorrhage was similar to that for an overt hemorrhage according to Moriarity et al. and a Type 1 lesion according to Zabramski et al.

Radiological Data

The brain MRI study performed closest to the time of diagnosis was reviewed, and imaging information was recorded for each patient. Location and diameter (at widest point) were recorded for each ICM on T2-weighted MR images. Any association with a venous angioma or other vascular malformation was also noted, although not all patients had contrast-enhanced MR images. In addition, multiplicity was noted. If there were multiple lesions and no symptomatic lesion, the size and location of the largest lesion was recorded. Follow-up brain MR images were reviewed when available.

Statistical Analysis

Descriptive statistics, including means, standard deviations, and frequencies, were used for patient characteristics and presenting symptoms. A comparison of proportions was performed using Fisher’s exact test with significance at p < 0.05. The prospective hemorrhage rate was determined as the number of definitive and probable prospective hemorrhages during the follow-up period divided by the number of prospective person-years of follow-up (an incidence rate); the annual rates were presented as the percentage per person-year. Patients were censored from this calculation if they underwent complete surgical removal of the ICM, but not if they underwent Gamma Knife treatment.

A Kaplan-Meier mortality curve for this group of patients with ICM was compared with that for an age- and sex-matched United States population.

Results

The prospective hemorrhage rate for our cohort of 110 patients, according to prospective follow-up via paper survey, phone survey, and/or clinical record review through 2003, was approximately 0.32% per year overall. Three patients were removed from this initial group based on criteria put forth by the angiomatosis alliance in 2008. These 3 patients were reclassified as having focal neurological deficit not otherwise specified. Thus, 107 patients (49.5% male) were included in our cohort and surveyed in the 2011–2012 time period. The remaining 182 patients had symptoms definitively related to the ICM including seizure, intracerebral hemorrhage, or focal neurologic deficits.

The mean age at diagnosis was 52.4 ± 19.9 years (mean ± standard deviation). Demographic features of this group are noted in Table 1. Patients in this group included those whose symptoms were clearly unrelated to the ICM (95 patients) and those who presented with symptoms having an unclear relationship to the ICM (12 patients). The latter patients typically had seizure disorders due to an alternative etiology (encephalitis, head trauma, generalized epilepsy syndrome, hippocampal atrophy) or were those about whom practitioners had differing clinical opinions regarding the relationship between the ICM and symptoms.

Intracerebral CMs were diagnosed using MRI in all patients, and 98 patients (92%) had MRI studies available.
for review by the primary investigator (K.D.F.). Radiologically, 95 patients (88.8%) had a single CM and 12 (11.2%) had multiple CMs. The location and type of ICM and its association with venous angiomas are noted in Table 2. The median duration of follow-up from the previously published data was 6.3 years (range 6 months–13 years, 610 person-years). With the updated follow-up through 2011–2012, the median follow-up was 12.5 years (range 6 months–25 years, 1311 patient-years). Eighty-seven patients (81%) had more than 5 years of follow-up. Forty-four patients were dead at the last follow-up.

The findings of this study reveal the very low risk of rupture in patients in whom an ICM is found incidentally, with no significant difference in mortality compared with that in age- and sex-matched controls. These data are used-

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### Table 1: Summary of demographic information for 107 patients with an ICM*

<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>males</td>
<td>49 (45.8)</td>
</tr>
<tr>
<td>mean age at diagnosis in yrs</td>
<td>52.4 ± 19.9</td>
</tr>
<tr>
<td>patients w/ hypertension</td>
<td>22 (20.6)</td>
</tr>
<tr>
<td>reason for MRI†</td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td>27 (25)</td>
</tr>
<tr>
<td>neoplastic disease</td>
<td>15 (14)</td>
</tr>
<tr>
<td>degenerative disease</td>
<td>16 (15)</td>
</tr>
<tr>
<td>acquired brain injury</td>
<td>20 (19)</td>
</tr>
<tr>
<td>seizure</td>
<td>11 (10)</td>
</tr>
<tr>
<td>other</td>
<td>18 (17)</td>
</tr>
<tr>
<td>patients w/ antithrombotic use at most recent FU‡</td>
<td>29/63 (46)</td>
</tr>
<tr>
<td>patients w/ history of cranial radiation</td>
<td>9 (8.4)</td>
</tr>
<tr>
<td>patients w/ history of brain biopsy prior to diagnosis</td>
<td>8 (7.5)</td>
</tr>
</tbody>
</table>

* FU = follow-up.
† Headache includes migraine, trigeminal neuralgia, or tension headache; neoplastic disease includes patients with primary brain tumors or those in whom MRI was done as a screen for metastatic disease; degenerative disease includes dementia, mental status changes, progressive gait imbalance due to degeneration, or Parkinson’s disease; acquired brain injury includes stroke, multiple sclerosis, head trauma; seizure includes those with seizure due to a cause other than ICM; and other includes various neurological clinical symptoms not referable to the ICM such as vertigo, hearing loss, visual complaints, and indeterminate spells.
‡ Forty-four patients were dead at the last follow-up.

### Table 2: Radiographic data in 107 patients with ICMs*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>single CM</td>
<td>95 (88.8)</td>
</tr>
<tr>
<td>location of ICM</td>
<td></td>
</tr>
<tr>
<td>cortical</td>
<td>60 (56.1)</td>
</tr>
<tr>
<td>supratentorial-subcortical</td>
<td>22 (20.6)</td>
</tr>
<tr>
<td>infratentorial</td>
<td>25 (23.4)</td>
</tr>
<tr>
<td>associated venous angioma</td>
<td>23 (21.5)</td>
</tr>
</tbody>
</table>

* In patients with multiple lesions, the largest asymptomatic lesion was used.

Two patients had brain hemorrhage after diagnosis of the ICM, and one of them had an undocumented cerebrovascular accident. One patient (0.9%) had a definitive prospective symptomatic hemorrhage due to ICM after the malformation’s initial diagnosis was confirmed both radiographically and clinically. A second patient with significant vascular risk factors died, and the death certificate listed “cerebrovascular accident” as the immediate cause of death and “AVM” as a secondary cause. Images in this case could not be obtained, and thus the case was considered an undocumented potential hemorrhage. An additional patient had a brain hemorrhage, but imaging clearly showed it was remote from the site of the ICM. If one includes only the definite or probable clinically symptomatic hemorrhages in the prospective hemorrhage rate, the overall annual risk of hemorrhage is 0.08% per patient-year. If one includes the undocumented potential hemorrhage, the rate is 0.15% per patient-year. Given the low rate of bleeding in this group, risk factors could not be analyzed.

The patient in whom the definitive prospective hemorrhage due to ICM was diagnosed had a familial form of CM. When the patient was 19 years old, a pineal tumor had been diagnosed, and he underwent resection and radiation in 1983 before the widespread use of MRI. In 1989, he underwent follow-up imaging, and multiple lesions believed to be CMs were noted. In the years after his tumor treatment, he required a ventriculoperitoneal shunt and multiple revisions. He remained disabled due to the tumor, radiation, and multiple shunt revisions. In 1999, he had a symptomatic hemorrhage from an ICM and underwent resection of the symptomatic lesion. Of note, CMs were diagnosed in his mother and sister during the follow-up period. No genotyping was performed.

The patient with an undocumented cerebrovascular accident presented to neurology at the age of 76 years for poor balance and possible normal-pressure hydrocephalus. He also had a frontal mass believed to be a CM measuring 3 × 4 cm. The neurologist and neurosurgeon believed that the patient, who also had a history of hypertension and hyperlipidemia, probably had a degenerative disorder and that the ICM was incidental.

None of the patients in this study experienced new seizures after the ICM was diagnosed.

Mortality for the study cohort compared with age- and sex-matched controls is noted in Fig. 1. While there was a trend toward increased mortality in the ICM group, it was not statistically significant (p = 0.08). The cause of death was ascertained in 34 patients (77%). No patient definitely died due to the ICM. As noted above, 1 patient died from a cerebrovascular accident, with AVM as a secondary cause. Images in this case could not be obtained, and thus it was impossible to determine if this patient had an ischemic or a hemorrhagic event.

### Discussion

The findings of this study reveal the very low risk of rupture in patients in whom an ICM is found incidentally, with no significant difference in mortality compared with that in age- and sex-matched controls. These data are use-
Hemorrhage rate in incidental cavernous malformations

Fig. 1. Kaplan-Meier curve comparing the mortality of patients with incidental ICM (thicker black line, “observed”) to that in a United States age- and sex-matched cohort (thinner gray line, “expected”).

ful to the clinician in counseling patients and comparing rupture risk with the surgical risk. The findings may impact the necessity for repeat imaging, surgical considerations, and questions patients may have about life expectancy.4 It is possible that some CMs form and bleed or become symptomatic immediately, whereas others form and stabilize and are more benign or “inactive.”18

A few other studies1,3,9,10 have demonstrated a low risk for prospective hemorrhage in patients presenting without hemorrhage, although the authors did not separate those patients in whom the ICM was found incidentally. These studies were also limited in their follow-up. The present study has the longest range of follow-up among any prior ICM natural history studies. It also emphasizes that patients with incidentally found ICMs should not be grouped with those having symptoms when studying the natural history of ICM, as the risk of rupture is quite different in symptomatic as compared with asymptomatic patients.3,7

There were too few clinical events to identify any statistically significant characteristics that would predict future rupture in this group of initially asymptomatic patients. However, the patients who did bleed from an ICM had multiple ICMs and underwent MRI for a pineal mass early in life. Patients typically present in their 20s–40s. Thus, in a patient with multiple lesions or the familial form of ICM and in whom the ICMs are found incidentally early in life, the natural history may be more uncertain and potentially more aggressive. Eleven percent of our population had multiple ICMs. None underwent genetic testing. Thus, the natural history data presented here are most applicable to patients with sporadic, rather than multiple, ICMs, and the patients with multiple ICMs deserve further study.

The mortality rate for patients with incidental ICM was not statistically different from that in an age- and sex-matched control group. The trend for an increased mortality rate in patients with ICM was due in part to their neurological comorbidities (dementia, brain tumors, and multiple sclerosis) that required imaging.

There are several limitations to this study. Because of the long follow-up, some patients could not be contacted, or death certificates were not available. Thus, we may have missed patients with potential rupture, underestimating the total rupture rate. As mentioned above, data may apply mainly to the group with sporadic ICMs, and caution should be exercised in applying the data to the familial form given the low representation of patients with multiple ICMs. It is also possible that tertiary care referral bias may influence this study. Typically, patients with symptomatic lesions are referred to tertiary care centers. Thus, the data provided here could also overestimate the symptomatic rates in that respect.

Conclusions

Patients with an incidental ICM probably have a very low risk of future hemorrhage and no significant change in mortality as compared with that in age- and sex-matched controls. These data may be most applicable to those with a single ICM. This information may be helpful to patients, clinicians, and insurers.

Disclosure

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