Metastases to hemangioblastomas in von Hippel–Lindau disease

S. TAYLOR JARRELL, M.D., ALEXANDER O. VORTMEYER, M.D.,
W. MARSTON LINEHAN, M.D., EDWARD H. OLDFIELD, M.D., AND RUSSELL R. LONSER, M.D.

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, and Urology Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and Department of Neurosurgery, The George Washington University Medical Center, Washington, DC

Object. Patients with hereditary cancer syndromes may be at increased risk for the development of tumor-to-tumor metastases. To gain insight into the biological nature of these lesions in the central nervous system (CNS), to determine their prevalence in a familial neoplasia syndrome, and to better define their management, the authors retrospectively examined a series of cases in which metastatic lesions developed within hemangioblastomas in patients with von Hippel–Lindau (VHL) disease.

Methods. The study included all cases of VHL disease in which patients underwent resection of a CNS hemangioblastoma that contained a metastasis or were found at autopsy to have a metastasis to a hemangioblastoma between January 2002 and December 2005 at the National Institute of Neurological Disorders and Stroke (NINDS). Clinical, histopathological, imaging, and surgical and/or autopsy findings were analyzed.

Metastasis to a CNS hemangioblastoma was found in six resected tumors (8% of all hemangioblastomas resected from patients with VHL disease at the NINDS during the study period) from six patients (five women, one man; mean age at surgery 42.5 years). The primary site of metastatic disease was the kidney in five patients (renal cell carcinoma) and the pancreas in one (a pancreatic neuroendocrine tumor). Only one patient had systemic metastases at the time of resection of the hemangioblastoma containing the metastasis. Neurologically, all patients had remained at baseline or were improved at last clinical follow-up examination (mean follow-up duration 16.5 months, range 3–40 months). In all cases, postoperative imaging revealed that the hemangioblastoma resection was complete, and there was no evidence of recurrence in any of the patients at the last follow up. Two patients (including one who was also in the surgical group) were found at autopsy to have CNS metastases exclusively to spinal hemangioblastomas.

Conclusions. Hemangioblastomas are an early and preferred site for metastasis in VHL disease. Emerging histopathological techniques may lead to recognition of an increasing number of cases of tumor-to-hemangioblastoma metastasis. Management of cases involving tumor-to-hemangioblastoma metastases in VHL disease should be based on the histological characteristics of the primary tumor, extent of the primary disease, and completeness of the resection.

KEY WORDS • hemangioblastoma • metastasis • tumor-to-tumor metastasis • von Hippel–Lindau disease

Metastasis to the CNS is a frequent complication of systemic malignancy. The incidence of metastatic brain tumors diagnosed in the US has been estimated to be as high as 170,000 cases a year. In their review of an autopsy series of 2375 patients with systemic malignancies, Posner and Chernik found that 24% of the patients had CNS metastases and that these lesions often involved the neural parenchyma, leptomeninges, and spinal epidural spaces. Consistent with hematogenous dissemination of malignant cells, metastases to the CNS are most frequently found at the junctions of gray and white matter and in distal arteries, where conditions are particularly conducive to neoplastic cell seeding, metastasis initiation, and growth.

Although metastases to the CNS are typically limited to normal neural and support tissues, involvement of a pre-existing CNS tumor by metastatic deposits from a systemic neoplasm may occur and is defined as “tumor-to-tumor metastasis.” Because patients with VHL disease frequently have visceral malignancies and multiple CNS hemangioblastomas, they are at increased risk for metastases to hemangioblastomas and thus may provide an excellent biological model to study this phenomenon. To gain insight into the biological nature of tumor-to-tumor metastases in the CNS, to determine their incidence in a familial neoplasia
syndrome, and to better define their management, we examined a series of cases of VHL disease in which tumor-to-hemangioblastoma metastases occurred.

Clinical Material and Methods

Surgical Cases

Patient Population. The study group included all patients with VHL disease who underwent resection of a CNS hemangioblastoma that harbored a metastasis between January 2002 and December 2005 at the NINDS. Because one of the patients (Case 6) in this group died during the follow-up period and additional metastases were found within another hemangioblastoma at autopsy, his case is reviewed in both the autopsy series and the surgical series.

Clinical Examination. Neurological examinations were conducted in detail at initial screening, immediately before and after an operation, and at approximately 6-month intervals after surgery. Findings from inpatient charts, clinic notes, and operative reports were recorded. Resection of a hemangioblastoma was performed if a patient was experiencing signs or symptoms attributable to a specific tumor.

Imaging Studies. To determine the extent of CNS involvement by hemangioblastomas, we obtained serial pre- and postoperative T1-weighted MR images of the craniospinal axis with and without contrast in all patients, using a 1.5-tesla MR unit (General Electric Medical Systems, Milwaukee, WI). Hemangioblastoma volumes were calculated by measuring the largest diameter in all three coordinate planes, then computing the volume according to the following formula: volume = width × height × length × 0.5.25,26 The tumors were serially sectioned and stained with H & E for morphological evaluation. Immunohistochemical staining for EMA and neuron-specific enolase was performed on all hemangioblastomas, and the tumor tissue sections were also stained with CD31 and/or CD34 to reveal the pattern of vascularization. When indicated, additional immunohistochemical staining was performed for cytokeratin AE1/AE3, synaptophysin, and CD10.

Results

Surgical Cases

Patient Characteristics. Six patients (five women and one man) with VHL disease underwent resection of a CNS hemangioblastoma that contained a metastasis during the study period. These six tumors accounted for 8% of all hemangioblastomas removed from patients with VHL disease during the study period at our institution. All six patients met the clinical criteria for VHL disease.23 They had a variety of visceral neoplasms associated with the syndrome, including RCCs (six patients, 100%), a pheochromocytoma (one patient, 17%), and a pancreatic neuroendocrine tumor (one patient, 17%) (Table 1, Fig. 1). Patients all had multiple CNS hemangioblastomas at the time of resection. Preoperatively, all patients had symptoms from the hemangioblastomas. Signs and symptoms included headache, pain, swallowing difficulties, sensory loss, weakness, and ataxia. The patients’ mean age at surgery was 42.5 years (range 28–60 years).

Imaging Findings. Three of the resected hemangioblastomas were located in the cerebellum and three were in the spinal cord. The mean tumor volume was 7.9 cm³ (range 0.3–21.9 cm³; Table 1). On preoperative contrast-enhanced MR images all six tumors appeared as well-demarcated, intensely enhancing lesions (Fig. 2), similar to CNS hemangioblastomas not affected by metastases. Peritumoral cysts or syringes were associated with three (50%) of the resected tumors. All tumors exhibited growth on serial MR images before resection.

Intraoperative Findings. On resection, the hemangioblastomas were found to be red-orange and well circumscribed. Five of the hemangioblastomas had no gross features that indicated they contained a metastasis, but in one patient (Case 6), a tan metastasis was visible through a thin layer of hemangioblastoma tissue during resection (Fig. 3). Sharp division of the hemangioblastoma tissue revealed a well-circumscribed, pea-sized, tan metastasis surrounded by red hemangioblastoma tissue.

Histopathological Findings. Histological examination of the resected hemangioblastomas revealed that a metastatic nidus was partially or completely enclosed by a rim of hemangioblastoma tissue in all six surgical specimens (Figs. 3 and 4). In each case, the metastatic tissue within the hemangioblastoma was determined to be histologically compat-
ble with the primary carcinoma. Whereas a single deposit of metastatic disease was found in all five hemangioblastomas containing RCC metastases, two metastatic foci (Fig. 2) were contained in a single cerebellar hemangioblastoma in the patient with a primary pancreatic neuroendocrine tumor (Case 4).

Although RCCs and hemangioblastomas frequently show overlapping architectural and cytological features, metastatic tumors could be clearly distinguished from surrounding hemangioblastomas. Metastatic RCC frequently had a distinct epithelial phenotype and showed strong anti-EMA immunoreactivity. To avoid inclusion of hemangioblastomas with focal EMA immunoreactivity, we further confirmed the presence of RCC metastases by demonstrating anti-CD10 and anti-AE1/AE3 (cytokeratin) reactivity. The two metastases from a pancreatic neuroendocrine tumor that were found in a cerebellar hemangioblastoma were also morphologically distinct from the surrounding hemangioblastoma tissue. In contrast to hemangioblastoma stromal cells, metastatic cells displayed robust anti-synaptophysin immunoreactivity (Fig. 2).

Clinical Results. All patients underwent complete resection of the hemangioblastoma, which was confirmed by postoperative MR imaging. At their most recent clinical follow-up examination (mean follow-up period 16.5 months, range 3–40 months), the neurological condition was found to be the same as at baseline in four patients and to have improved in two since resection of the lesions. In one of the six surgical cases (Case 4; Table 1), the patient had pancreatic neuroendocrine tumor metastases to a hemangioblastoma. She underwent partial resection of a 10-cm pancreatic neuroendocrine tumor 66 months before resection of the CNS hemangioblastoma. At the time of surgery for the CNS hemangioblastoma, CT imaging revealed a 2.5-cm primary pancreatic tumor and multiple metastases in the liver. These metastases were successfully treated with percutaneous ablation. Six months after resection of the hemangioblastoma and the metastases within it, a metastatic lesion developed in the patient’s scapula. This lesion was completely resected. At last follow up, 12 months after the CNS surgery, the patient has no evidence of new metastases.

In the other five surgical cases (Cases 1–3, 5, and 6), the patients had RCC metastases to hemangioblastomas. Serial surveillance imaging of visceral lesions in these patients has revealed no evidence of primary disease progression or metachronous metastases in four cases (Cases 1–3, and 5) and no adjuvant therapy (chemotherapy or radiation therapy) has been required. In the fifth case (Case 6), resection of a large (6.7-cm) RCC and adjuvant therapy were recommended after removal of a hemangioblastoma containing an

### TABLE 1

Surgical and autopsy cases of metastasis to hemangioblastoma in patients with VHL disease*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Hemangioblastoma Location†</th>
<th>Size (cm³)</th>
<th>Primary Tumor (diameter [cm])</th>
<th>Other Sites of Metastases</th>
<th>Other Non-CNS Tumors‡</th>
<th>Symptoms</th>
<th>FU (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 36, F</td>
<td>sacral</td>
<td>21.9</td>
<td>RCC (1)</td>
<td>none</td>
<td>none</td>
<td>buck &amp; lower extremity</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>2 60, F</td>
<td>cerebellar</td>
<td>0.4</td>
<td>RCC (2.4)</td>
<td>none</td>
<td>pheochromocytoma</td>
<td>headache</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>3 46, F</td>
<td>cerebellar</td>
<td>6.0</td>
<td>RCC (1.0)</td>
<td>none</td>
<td>retinal hemangioblastoma</td>
<td>weakness, ataxia, difficulty swallowing</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>4 28, F</td>
<td>cerebellar</td>
<td>3.6</td>
<td>pancreatic neuroendocrine tumor (2.5)</td>
<td>none</td>
<td>ELST, RCC</td>
<td>headache</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>5 44, F</td>
<td>thoracic</td>
<td>14.8</td>
<td>RCC (1.6)</td>
<td>none</td>
<td>retinal hemangioblastoma</td>
<td>pain</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6§ 41, M</td>
<td>thoracic</td>
<td>1.0</td>
<td>RCC (6.7)</td>
<td>none</td>
<td>none</td>
<td>lower-extremity weakness, sensory loss</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>50, F lumbar</td>
<td>5.6</td>
<td>RCC (4.1)</td>
<td>none</td>
<td>pheochromocytoma, pancreatic neuroendocrine tumor</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* ELST = endolymphatic sac tumor; FU = follow up; NA = not applicable.
† Site of metastasis to hemangioblastoma identified at surgery or autopsy.
‡ That is, non-CNS tumors associated with VHL disease and harbored by the patients in addition to the primary tumor that was the origin of the metastasis. All surgical patients also had other CNS hemangioblastomas in addition to the one removed.
§ This patient underwent resection of a thoracic hemangioblastoma that contained an RCC metastasis. Four months later he died of progressive systemic disease. At autopsy two additional RCC metastases to hemangioblastomas were found in the spinal cord.
|| This patient died of a spontaneous hemorrhage from a cerebellar hemangioblastoma. At autopsy, a lumbar hemangioblastoma that contained an RCC metastasis was discovered.

![Fig. 1. Case 3. Axial contrast-enhanced CT scans of the abdomen demonstrating multiple, bilateral, enhancing RCCs (arrows) in this patient with VHL disease in whom RCC metastasized to a cerebellar hemangioblastoma.](image-url)
RCC metastasis, but the patient declined, and the primary RCC progressed, resulting in bowel obstruction that led to his death 4 months later. Computed tomography studies of his chest, abdomen, and pelvis obtained 1 week before his death revealed disease progression at the primary tumor site and bilateral lung metastases.

Autopsy Cases

Cases. After the deaths of two patients with VHL disease (Cases 6 and 7) an autopsy examination was performed during the study period (Table 1). Both patients met the clinical criteria for VHL disease. In one case (Case 6), the patient died of progressive systemic disease 4 months after resection of a thoracic hemangioblastoma that contained an RCC metastasis (see previous section). The patient in the other autopsy case (Case 7) died at another institution after spontaneous hemorrhage from a cerebellar hemangioblastoma.

Autopsy Findings. In the first autopsy case (Case 6), a large primary RCC (6.7 cm diameter) was found in the remaining kidney, and RCC metastases were found in the lungs. One cerebellar and four spinal cord hemangioblastomas (that is, a total of five CNS hemangioblastomas) were identified in this patient, and two of the spinal cord hemangioblastomas contained metastatic RCC deposits (confirmed morphologically and immunohistochemically; Fig. 4).

In the second autopsy case (Case 7) a large cerebellar hemorrhage associated with a cerebellar hemangioblastoma was found. Despite a detailed microscopic examination, no evidence of metastatic cells could be found in the intraparenchymal clot or the associated hemangioblastoma. Examination of the viscera revealed a large primary RCC (4.1 cm in diameter) in the right kidney, a pheochromocytoma, and a pancreatic neuroendocrine tumor (Table 1). Five hemangioblastomas were found in the CNS (two in his cerebellum, three in the spinal cord), and one of the spinal cord hemangioblastomas contained a metastatic RCC deposit (confirmed morphologically and immunohistochemically).

Discussion

Definition of Tumor-to-Tumor Metastasis

In 1984, Pamphlett defined the criteria for diagnosis of tumor-to-tumor metastasis. He established three criteria. 1) The metastatic nidus must be at least partially enclosed by a rim of histologically distinct primary tumor tissue. 2) The existence of the primary carcinoma must be proven. 3) The metastatic tumor must be demonstrated to be compatible with the primary carcinoma by morphological or immunohistochemical means. Each of the cases described in this series met these criteria for tumor-to-tumor metastasis. Specifically, all patients had metastasis to a CNS hemangioblastoma from a visceral tumor associated with VHL disease.

Von Hippel–Lindau Disease

Von Hippel–Lindau disease is an autosomal-dominant neoplasia syndrome that is caused by a germline mutation or deletion on the short arm of chromosome 3. The syndrome is characterized by the development of visceral and CNS lesions. The visceral lesions include RCCs (24–45% of patients), renal cysts (25–60% of patients), pheochromocytomas (10–20% of patients), pancreatic cysts (40–91% of patients), and pancreatic neuroendocrine tumors (35–70% of patients). Cystadenomas of the epididymis and broad ligament may also be present (25–60% of patients). Tumors of the CNS include hemangioblastomas (48–80% of patients) of the cerebellum (44–72%), brainstem (10–25%), spinal cord (13–50%), and retina (25–60%), as well as endolymphatic sac tumors (10–15% of patients).

The visceral tumors that are associated with VHL disease and have metastatic potential include RCCs, pheochromocytomas, and pancreatic neuroendocrine tumors. Indications for resection of each of these types of tumors differ in the setting of VHL disease. Previous work has shown a strong positive correlation between RCC size and metastatic potential. Duffey and colleagues followed up 108 pa-
patients with VHL disease and RCCs and reported that RCCs less than 3 cm in diameter did not metastasize, whereas those greater than 3 cm in diameter metastasized in 27% of patients. Based on these findings and multiplicity of RCCs in individual patients with VHL disease, many centers have advocated observation of RCCs less than 3 cm and resection of those larger than this size in patients with VHL disease. Most pheochromocytomas associated with VHL disease are removed as soon as convenient after diagnosis because of their potentially lethal systemic effects. According to Libutti and coauthors, \textsuperscript{22} resection of pancreatic neuroendocrine tumors is indicated in VHL disease if any of the following conditions are met. 1) There is no evidence of metastatic disease. 2) The lesion diameter is greater than 3 cm (\textsuperscript{2} cm if the lesion is in the pancreatic head). 3) The patient is undergoing a laparotomy for treatment of another visceral manifestation of VHL disease.

Previous Reports of CNS Tumor-to-Tumor Metastasis

Tumor-to-tumor metastasis is a recognized but rare occurrence in the CNS. In 1930, Fried\textsuperscript{12} first described a metastasis to a primary intracranial tumor (a metastasis from a lung carcinoma to a meningioma). Subsequent descriptions have shown that meningioma is the most common CNS recipient tumor (83% of reported cases of metastasis to a CNS tumor) and breast and lung carcinomas are the most common metastatic tumors (79% of reported cases of metastases to the CNS).\textsuperscript{6} Rarer cases of metastasis to other CNS recipient tumors—including oligodendroglioma,\textsuperscript{11,37} anaplastic astrocytoma,\textsuperscript{27} glioblastoma,\textsuperscript{25} ependymoma,\textsuperscript{27} schwannoma,\textsuperscript{21,39,41} pituitary adenoma,\textsuperscript{11,36} and hemangioblastoma\textsuperscript{1,2,5,8,13,18,28}—have also been reported.

When metastasis to a primary CNS tumor occurs, it is frequently associated with synchronous metastases elsewhere. In their review, Chambers and colleagues\textsuperscript{7} reported that 23 (92%) of 25 cases of metastases to CNS meningiomas and acoustic neuromas were associated with metastases to other sites, including the lymph nodes, bones, brain, and liver. A recent review by Caroli, et al.,\textsuperscript{6} found synchronous metastases in 39 (62%) of 63 cases.

Previously, metastases to CNS hemangioblastomas have been reported in eight cases. In 1988, Crockard, et al.,\textsuperscript{8} described a patient who was found to have a prostate carcinoma metastasis to a residual sporadic cerebellar hemangioblastoma 1 year after initial resection of the hemangioblastoma. Seven cases of RCC metastases to cerebellar (four) or spinal cord (three) hemangioblastomas in patients with VHL disease have been reported.\textsuperscript{1,2,5,13,18,28} Consistent with our findings, synchronous metastases were detected in only two (29%) of these patients.

Current Report

Surgical and Autopsy Cases. The seven surgical and autopsy cases described in this paper all met the clinical criteria for VHL disease. In addition to harboring CNS hemangioblastomas, the patients had a variety of visceral neoplasms associated with VHL disease, including RCCs (seven; 100%), pheochromocytomas (two; 29%), and pancreatic neuroendocrine tumors (two; 29%) (Table 1). Metastases to hemangioblastomas included RCCs (eight tumors) and a pancreatic neuroendocrine tumor (one tumor), and the recipient hemangioblastomas were distributed throughout the cerebellum and spinal cord. The findings in these cases provide a number of insights into the biology, incidence, clinical characteristics, and implications for management of tumor-to-tumor metastases in the CNS.

Preferential RCC Metastasis to Hemangioblastoma. These cases demonstrate that hemangioblastomas may represent a preferred site of metastasis for RCC associated with VHL disease. Preoperative imaging did not reveal evidence of metastatic disease in any of the five patients in our surgical series who had RCC metastases to hemangioblastomas (Cases 1–3, 5, and 6). Four of these patients still had no evidence of metastatic disease at last follow up (mean follow-up period 19.2 months, range 12–40 months). The fifth patient (Case 6) died 4 months after surgery, and CT imaging
performed within 1 week of his death revealed progression of the primary tumor and lung metastases (findings that were confirmed at autopsy). Two additional RCC metastases to hemangioblastomas were discovered in the thoracic segment of his spinal cord (of a total of five CNS hemangioblastomas identified in this patient) at autopsy. In the second autopsy case (Case 7), there was an RCC metastasis to a lumbar spinal cord hemangioblastoma (of five CNS hemangioblastomas identified) but no evidence of systemic metastasis or other CNS metastases.

Several biological features of CNS hemangioblastomas may make them preferential sites for metastases. Hemangioblastomas associated with VHL disease are frequently multiple and slow growing (with quiescent periods extending for years), and they often remain asymptomatic, not requiring resection. Consequently, they are available to receive a metastasis for a prolonged period in the presence of other systemic malignancies. That the most frequently reported cases of tumor-to-tumor metastases in the CNS are metastases to benign meningiomas also suggests that time plays an important role. Hemangioblastomas are highly vascular tumors that may provide an ideal environment for metastatic seeding and development. The importance of vascularity in predisposing a site for metastasis is underscored by previous studies showing that metastases preferentially distribute to regions of high cerebral blood flow in the CNS, as well as by demonstration of preferential metastasis to the hypervascular rim of ischemic infarction. Finally, the impaired VHL protein function that occurs in hemangioblastomas associated with VHL disease disrupts fibronectin matrix assembly, potentially making these tumors particularly vulnerable to metastatic disease.

**Metastasis Type.** The type of metastasis that has been most often found within hemangioblastomas is RCC. This was the type of metastasis found in all previously reported cases of metastases to hemangioblastomas in patients with VHL disease and in six (89%) of our seven cases. Renal cell carcinoma is the most common visceral malignancy in VHL disease, but its preponderance in metastases to hemangioblastomas may be partially due to the way it is managed. Other visceral malignancies associated with VHL disease, including pheochromocytomas and pancreatic neuroendocrine tumors, are often resected after imaging or chemical diagnosis. However, to preserve renal function and to minimize the number of visceral surgeries patients must undergo, RCCs in VHL are frequently not treated until they reach a diameter of 3 cm. Consequently, an RCC nidus with the potential to disseminate malignant cells through the circulatory system may be present for years in patients with VHL disease. Four (67%) of six patients in this series had RCCs that were below the 3-cm treatment threshold.

**Incidence.** The six metastases to hemangioblastomas removed from the patients in the surgical cases described in this paper represent 8% of all CNS hemangioblastomas removed from patients with VHL disease at our institution during the study period. This incidence is significantly
greater than what would be expected based on the literature on tumor-to-tumor metastases in the CNS, including metastases in the setting of VHL disease. There are a number of potential reasons for our identification of a high occurrence of these lesions in our patients with VHL disease. In the setting of VHL disease, the combination of malignant visceral tumors and multiple slow-growing CNS hemangioblastomas provides an ideal environment for the development of metastases to hemangioblastomas. The occurrence of tumor-to-tumor metastases may previously have been underrecognized, particularly in VHL disease. Because RCCs and hemangioblastomas have similar morphological characteristics, the diagnosis of RCC metastasis within a hemangioblastoma may be overlooked, and RCCs are the most common metastatic tumors found in hemangioblastomas. Established and recently described histopathological techniques, including those applied to the tumors in the current series, may increase recognition of these lesions.

Preoperative Features. We were unable to identify, even in retrospect, any preoperative clinical or imaging features that could be used to diagnose metastases to hemangioblastomas. The tumors all vividly enhanced on MR imaging (Figs. 2–4), and peritumoral cysts (Fig. 2), which are frequently associated with CNS hemangioblastomas, were seen in 50% of the cases. Although all tumors exhibited growth on MR imaging before resection, hemangioblastomas that do not contain metastases occasionally have spurs of rapid growth, including rates of enlargement similar to the rates observed in the tumors containing metastases in the current series.

Outcome. At last clinical follow up (mean 16.5 months, range 3–40 months), all patients were found to have remained neurologically stable or to have improved in comparison to their preoperative neurological baseline. Postoperative MR imaging revealed complete resection of the hemangioblastomas in all cases.

In one of the six surgical cases (Case 4), the patient had pancreatic neuroendocrine tumor metastases within a hemangioblastoma. She had undergone partial resection of a 10-cm pancreatic neuroendocrine tumor 66 months before undergoing resection of the CNS hemangioblastoma. At the time of surgery for the CNS hemangioblastoma, CT imaging revealed a 2.5-cm residual primary pancreatic tumor and multiple metastases to the liver. These metastases were successfully treated with percutaneous ablation. Six months after resection of the hemangioblastoma and associated metastases, a metastatic lesion was found in her scapula. It was completely resected. At last follow up (12 months after the CNS surgery), no evidence of new metastases was detected.

In the remaining five surgical cases (Cases 1–3, 5, and 6), the patients harbored RCC metastases within hemangioblastomas. Serial surveillance imaging of visceral lesions has revealed no evidence of progression of primary disease or metachronous metastases in four of these patients (Cases 1–3 and 5), and additional treatment (primary site resection, chemotherapy, and/or radiation therapy) has not been undertaken. Because the fifth patient (Case 6) with an RCC metastasis to a hemangioblastoma had a large primary RCC (6.7 cm) that exceeded the threshold for surgical treatment, excision of the primary tumor and adjuvant therapy were recommended. The patient declined the recommended treatment, and the primary RCC tumor progressed, resulting in bowel obstruction that led to his death 4 months later. Computed tomography images of his chest, abdomen, and pelvis obtained 1 week before his death revealed progression of the primary tumor and bilateral lung metastases (findings that were confirmed at autopsy).

Implications for Management. Because imaging did not detect metastases to hemangioblastomas, the diagnosis was based on histopathological findings. Whenever CNS hemangioblastomas are removed from patients with VHL disease who are known to have visceral malignancies, complete and detailed histological analyses should be performed on the tumors to determine whether they contain metastatic lesions. Continued serial follow-up imaging may be appropriate for patients who undergo complete resection of an RCC metastasis to a hemangioblastoma and harbor a primary RCC that is less than 3 cm in diameter. In patients with VHL disease who have other types of metastases to hemangioblastomas, decisions regarding treatment of the primary tumor should be based on the histological characteristics of the tumor, the extent of the disease process, and the completeness of resection of the hemangioblastoma containing the metastasis.

Conclusions

For several reasons, hemangioblastomas are an early and preferred site for metastasis in VHL disease. Tumor-to-hemangioblastoma metastasis in patients with VHL disease may be an underrecognized phenomenon, and emerging immunohistochemical techniques may lead to recognition of an increasing number of these cases. Management of cases involving tumor-to-hemangioblastoma metastases in VHL disease should be based on the histological characteristics of the primary tumor, the extent of the primary neoplastic disease, and completeness of resection of the hemangioblastoma containing the metastasis.

Acknowledgments

We thank Hetty L. DeVroom, R.N., and Rene K. Smith, R.N., for their invaluable contributions to our clinical research program for patients with VHL disease and Cindy Taylor for her outstanding help with tissue preparation and immunohistochemical support.

References

6. Caroli E, Salvati M, Giangaspero F, Ferrante L, Santoro A: Intra-
Metastasis to hemangioblastoma

meningioma metastasis as first clinical manifestation of occult primary breast carcinoma. Neurosurg Rev 29:49–54, 2005

Manuscript received December 23, 2005. Accepted in final form February 20, 2006. This research was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. Address reprint requests to: Russell R. Lonser, M.D., Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 5D37, Bethesda, Maryland 20892-1414. email: lonserrr@ninds.nih.gov.