Renal Cell Carcinoma to the Pancreas in Surgical Pathology Material

A Clinicopathologic Study of 21 Cases with a Review of the Literature

Lester D. R. Thompson, M.D.
Clara S. Heffess, M.D.

Department of Endocrine and Otorhinolaryngic-Head & Neck Pathology, Armed Forces Institute of Pathology, Washington, D.C.

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Address for reprints: Lester D. R. Thompson, M.D., Chief, Otorhinolaryngic-Head and Neck Division, Department of Endocrine and Otorhinolaryngic-Head and Neck Pathology, Building 54, Room G066-11, Armed Forces Institute of Pathology, 6825 16th Street, NW, Washington, DC 20306-6000; fax: 202-782-3130; E-mail: thompsonl@afip.osd.mil.

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BACKGROUND. Clear cell carcinomas of the pancreas are rare and more likely represent metastatic renal cell carcinoma (RCC).

METHODS. Twenty-one cases of metastatic RCC to the pancreas were retrieved from the files of the Endocrine Registry of the Armed Forces Institute of Pathology. Histologic features were reviewed, special stains and immunohistochemical studies were performed, and patient follow-up data were obtained.

RESULTS. The patients included 9 women and 12 men ages 47–76 years (mean, 64.4 years). Patients experienced weight loss, abdominal pain, or a mass lesion. The tumors occurred anywhere within the pancreas. The mean size of the tumors was 4.0 cm. Histologically, the tumors were comprised of clear cells with a rich vascular network. The RCC was diagnosed before (n = 17 patients; ages up to 32.7 years) or after (n = 4 patients; ages up to 13.2 years) the pancreatic metastases were discovered. Surgery was used in all patients. Adjuvant chemotherapy was used in 4 patients. From the date of the diagnosis of pancreatic metastasis, 13 patients were dead with disseminated disease (DD) (mean, 4.5 years), and 8 patients were without disease (mean, 9.0 years). From the date of the diagnosis of primary RCC, 13 patients were DD (mean, 12.7 years), and 8 patients were without disease (mean, 24.7 years).

CONCLUSIONS. Although histochemical and immunohistochemical studies may help in the distinction between patients with primary versus metastatic clear cell tumors of the pancreas, clinical confirmation should be obtained. Surgical resection of the pancreatic metastatic disease is suggested, because the patient may still have a prolonged survival. ***Cancer* 2000;89:1076–88.**
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Pancreatic metastases uncommonly present in patients with malignant disease, especially in surgical pathology material. The majority of such cases offer vague and nonspecific clinical symptoms, including weight loss, fatigue, abdominal pain, and a mass lesion. Metastatic tumors to the pancreas, excluding those involved with widespread disease or in direct continuity with the pancreas, are rare clinically and are exceedingly difficult to differentiate from a primary pancreatic neoplasm. When metastatic foci to the pancreas clinically manifest as mass lesions, lung, breast, colon, skin (melanoma), and kidney primary tumors are among the metastatic neoplasms that are found most frequently.[1–58] Secondary involvement of the pancreas by metastatic renal cell carcinoma (RCC), especially in surgical pathology material, is rare. The distinction between clear cell primary pancreatic tumors and metastatic deposits of clear cells within the pan-

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creatic parenchyma may lead to clinical and pathologic diagnostic difficulties. The diagnostic dilemma is heightened further in patients in whom the metastatic deposit in the pancreas is the primary manifestation of an unknown primary tumor.

The clinical presentation of a solitary pancreatic mass simulates a pancreatic primary tumor. Whereas metastatic RCC to the pancreas has been reported previously,[1–58] the emphasis has rested on the clinical or radiographic presentation and not the histologic differential diagnosis. Many of these reports document superficially the types of tumors metastatic to the pancreas, but they do not address specifically RCC or the distinctive histologic features. The case reports and small series individually serve as valuable adjuncts to understanding the unusual metastatic pattern of RCC. However, a comprehensive analysis encompassing the use of clinical features (preoperative diagnosis), histologic findings (criteria for the recognition of metastatic RCC), immunophenotypic studies, and follow-up information applied to a group of patients with pancreatic metastatic RCC, to the best of our knowledge, is absent from the literature (MEDLINE, 1966–1999).

MATERIALS AND METHODS

Twenty-one cases of metastatic RCC to the pancreas were identified in the files of the Endocrine Registry at the Armed Forces Institute of Pathology from 1970 to 1997. These 21 cases were identified in a review of 8562 (0.25%) benign and malignant pancreatic neoplasms that were seen in consultation during this same period. Patients with secondary pancreatic tumors resulting from direct invasion from malignant tumors of the contiguous organs were omitted from this study, as were cases of systemic disease (lymphoma or leukemia). Sixteen cases were obtained from civilian sources, including university medical centers and foreign contributors, three cases were from military hospitals, and two cases were from Veterans Administration medical centers.

Materials within the Institute's files were supplemented by a review of the patient demographics, symptoms at presentation, and past medical and surgical history (specifically, a history of previous RCC or renal surgery). In addition, we reviewed radiographic, surgical pathology, and operative reports and obtained information from oncology data services by written questionnaires or direct communication with the treating physician(s). Follow-up data, which were available for all patients, included information regarding tumor location, treatment modalities, and current patient and disease status. All cases that were included in this study had histologic confirmation of RCC, although we were not consulted formally on all primary RCC diagnoses. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

Hematoxylin and eosin stained slides from all cases were reviewed for morphologic assessment of metastatic RCC. Periodic-acid Schiff (PAS) stain (with and without diastase digestion) and mucin stain (Mayer mucicarmine) were performed. Immunophenotypic analysis was performed in 13 cases with suitable material by using the standardized avidin-biotin method of Hsu et al.[59] employing 4-μm-thick, formalin fixed, paraffin embedded sections. Table 1 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block in each case. When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% protease VIII (Sigma Chemical Co., St. Louis, MO) in 0.1 M phosphate buffer, pH of 7.8, at 37 °C. Antigen enhancement (recovery) was performed as required by using formalin fixed, paraffin embedded tissue that was treated with a buffered citric acid solution and heated for 20 minutes in a calibrated microwave oven. After this, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 minutes before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were graded as weak (1+), moderate (2+), and strong (3+) staining, and the fraction of positive cells was determined by separating the percentage of positive cells into four groups: $<$ 1%, 1–10%, 11–50%, 51–90%, and $>$ 90%, specifically for the proliferation markers (Ki-67 and p53).

A review of English journal publications (MEDLINE, 1966–1999) was performed, and all reports of RCC to the pancreas that were identified in surgical pathology material were included in the review.[1–58] No foreign language articles were included. In all instances in this work in which the literature is referenced, it includes all of the writings cited in Table 2 unless an article is cited individually for a specific reason.

RESULTS

Clinical Demographics and Presentation

There were 9 women and 12 men, ages 47–76 years, with a mean of 64.4 years at the time of the pancreatic tumor presentation (Table 3). Whereas the mean age at presentation for women was older than men (69.0 years and 60.9 years, respectively), we do not have an explanation for this finding. Two groups can be cre-

TABLE 1
Immunohistochemical Panel

Antigen/antibody	Primary antibody	Company	Dilution	Antigen recovery
Cytokeratin (AE1/AE3 and CK1)	mm	Boehringer Mannheim Biochemicals, Indianapolis, IN, and Dako, Carpinteria, CA	1:50 1:200	Enzyme digestion
Cytokeratin 7	mm	Dako	1:200	Enzyme digestion
Cytokeratin 20	mm	Dako	1:50	Enzyme digestion
Epithelial membrane antigen	mm	Dako	1:100	Enzyme digestion
CAM 5.2	mm	Becton Dickinson, San Jose, CA	1:100	Enzyme digestion
CA19-9	mm	Signet Laboratories, Dedham, MA	Neat	Enzyme digestion
CEA	rp	Dako	1:800	Enzyme digestion
Vimentin	mm	BioGenex	1:400	n/a
Ki-67	mm	Immunotech, Westbrook, ME	1:20	Microwave recovery
p53	mm	Dako	1:50	Microwave recovery
gp200 Ab-1	mm	Neomarkers, Union City, CA	1:200	n/a

mm: mouse monoclonal; rp: rabbit polyclonal; CEA: carcinoembryonic antigen; n/a: not applicable.

ated by separating the patients based on type of presentation: RCC as the initial presentation and pancreatic tumor as the initial presentation. There were 17 patients in the first group and four in the second group. There were no appreciable differences between the groups when analyzing gender, age at presentation, or length of time with symptoms.

Patients presented with a mass lesion in the pancreas (n = 8 patients) in addition to abdominal pain (n = 7 patients). In an additional 9 patients, early satiety, weight loss, diarrhea, hematuria, nausea, constipation, or symptoms associated with chronic pancreatitis were identified. Five of the patients' tumors were discovered incidentally during routine physical examination or diagnostic surveillance radiographic studies performed as part of their oncology follow-up regimen. The symptoms lasted from 2 months to 36 months, with a mean of 8.1 months. The patients with a known renal carcinoma had a shorter mean duration of symptoms (6.3 months) than those patients without a known primary tumor (16.7 months). This difference may be related to more frequent physical examinations and radiographic studies for patients with a known RCC primary tumor as part of their follow-up. Furthermore, the overall longer mean duration of symptoms for patients without a known primary tumor may be related to the generally nonspecific nature of the initial presenting symptoms, which often were managed symptomatically without a specific diagnostic evaluation. There was no clinical evidence of diabetes mellitus in any of the patients.

Radiographic Studies

Eighteen of the patients had 1 or more of a variety of imaging procedures performed prior to surgery, including abdominal X-ray, ultrasonography, computer tomography (CT) scan, magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), and angiography. In general, a well-defined, solid to cystic, retrogastric mass was identified (by ultrasound and CT scan or MRI) predominantly involving the body and/or tail of the pancreas. Cross-sectional CT images identified multinodular parenchymal, solid to cystic masses, often enhancing with contrast media. Ultrasonography usually showed hypoechoic and cystic to solid mass(es). Obstructive findings were noted, including duct dilatation and common bile duct obstruction. Signs of chronic pancreatitis were observed in a few cases.

Pathology

Macroscopic findings

Slightly more patients presented with a solitary nodule in the pancreas (n = 11 patients) than with multifocal disease (n = 9 patients), although this was not of clinical significance (Table 4). The tumors occurred in the head alone (n = 6 patients), in the tail alone (n = 4 patients), in the body and tail (n = 7 patients), or randomly throughout the pancreas. The tumors ranged in size from 1.5 cm to 12.0 cm (mean, 4.0 cm). Macroscopically, the neoplasms usually were well defined and easily separated from the pancreatic parenchyma. The cut surface, when it was not submitted in multiple fragments, was comprised of brightly yellow-orange to white-gray, well-demarcated, and sharply circumscribed masses. A few of them were partly necrotic and hemorrhagic fluid-filled cysts. Occasionally, infiltrating into the substance of the pancreas, a few nodules were described as fixed to the surrounding structures. The primary RCC affected the left kidney in

TABLE 2
Metastatic Renal Cell Carcinoma to the Pancreas Identified in Surgical Pathology Material: Review of the English Literature[a]

All patients (n = 109)[a]	No.
Gender	
Women	32
Men	39
Not reported	38
Age at presentation of metastasis (yrs)	
Range	32–82
Mean	62.0
Females (mean)	61.9
Males (mean)	62.2
Type of presentation	
Pain	16
Weight loss, fatigue, malaise	13
Anemia, melena, hematochezia, hematemesis, hematuria (bleeding)	10
Mass	4
Jaundice	5
Other (nausea, pancreatitis, cough, diabetes mellitus, regurgitation, diarrhea)	15
Asymptomatic (diagnostic evaluation)	17
Primary site	
Right kidney	23
Left kidney	23
Bilateral	8
Not reported	55
Metastatic site within pancreas	
Head	26
Tail	9
Diffuse	11
Body	6
Body and tail (multifocal masses)	6
Head and tail (multifocal masses)	5
Head and body (multifocal masses)	4
Tumor size (cm)	
Range	1–18
Mean	4.9
Interval from nephrectomy (primary resection)	
Synchronous	16
Range (yrs)	0.5–27
Mean (yrs)	8.4
Outcome	
Alive, no evidence of disease (mean yrs of follow-up)	33 (1.3)
Alive, no further specified (mean yrs of follow-up)	7 (1.3)
Dead, no evidence of disease (yrs of follow-up)	1 (1.2)
Dead with disseminated disease (mean yrs of follow-up)	9 (0.7)
Not reported	59

[a] See References 1–58.

[b] The parameter was not always stated in the report; therefore, the numbers do not necessarily equal the total values shown in the columns.

TABLE 3
Clinical Features of Metastatic Renal Cell Carcinoma to the Pancreas

		Clinical presentation	
Feature	All	Renal cell carcinoma as primary presentation	Pancreas tumor as primary presentation
All patients	21	17	4
Gender			
Women	9	7	2
Men	12	10	2
Age in yrs at presentation (mean)			
All	64.4	64.5	64.0
Women	69.0	67.9	73.0
Men	60.9	62.1	55.0
Length of symptoms (months)			
Range	2.0–36	2.0–36	6.0–36
Mean	8.1	6.3	16.7
Type of presentation[a]			
Mass	8	5	3
Pain	7	7	—
Early satiety, weight loss, diarrhea, hematuria, nausea, constipation, chronic pancreatitis	9	8	1
Diagnostic examination or asymptomatic	5	4	1

[a] Patients may have presented with more than one symptoms; therefore, the numbers do not add up to the total number of patients.

TABLE 4
Macroscopic Features

Feature	All	Renal cell carcinoma as primary presentation	Pancreas tumor as primary presentation
Type of presentation			
Solitary mass	11	9	2
Multifocal masses	9	7	2
Unknown	1	1	—
Anatomic location			
Head	6	4	2
Tail	4	4	—
Body and tail	7	6	1
Entire pancreas	4	3	1
Tumor size (cm)			
Range	1.5–12.0	1.5–12.0	2.5–6.0
Mean	4.0	4.0	4.1

12 patients and the right kidney in 7 patients, whereas the particular side was unknown in 2 patients. None of the patients developed bilateral tumors.

Microscopic findings

The neoplastic deposits usually were well-circumscribed or even encapsulated and were separated distinctly from the pancreatic parenchyma (Fig. 1). Although they were well circumscribed in the majority of cases, the cells occasionally were identified invading the surrounding pancreas. The predominant histologic pattern was characterized by the presence of sheets, small nests, and cords of neoplastic cells sep-

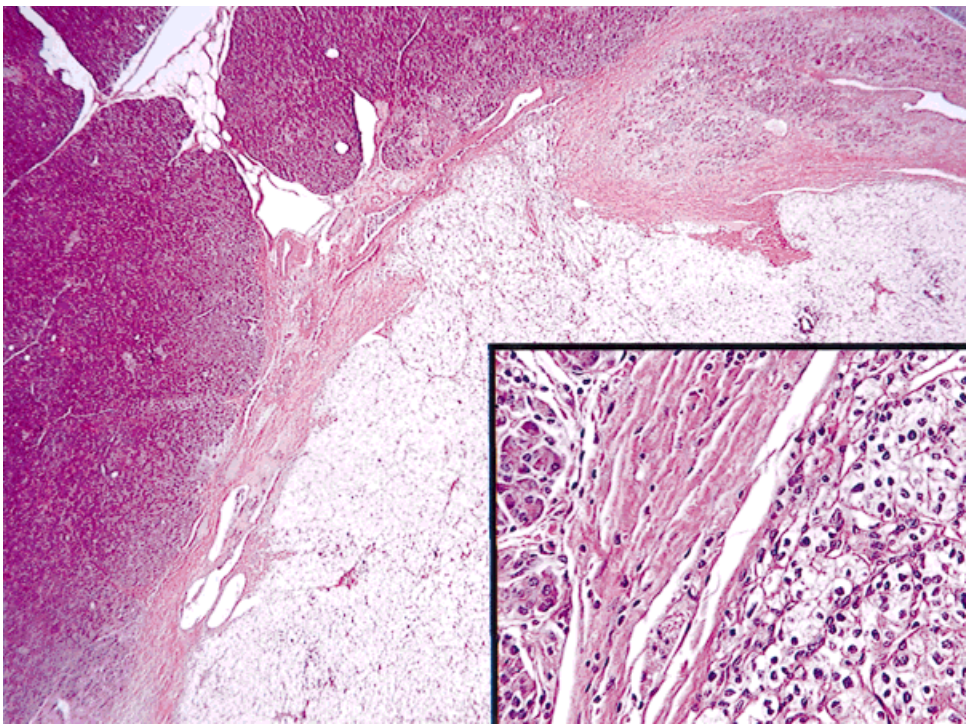

FIGURE 1. Low power illustration of an encapsulated nodule of metastatic renal cell carcinoma in the pancreas. The inset demonstrates close proximity to the surrounding pancreatic parenchyma.

arated by a prominent vascular stroma. A papillary pattern was not identified.

The neoplastic deposits were composed of polygonal or elongated cells with clear cytoplasm, distinct cytoplasmic membranes, and small, compact, eccentric nuclei (Fig. 2). Nuclear pleomorphism was minimal to nonexistent in the majority of cases, with only three cases demonstrating an increased nuclear grade (Fig. 3). Whereas clear cell features were the dominant finding in all cases, foci of cells with slightly eosinophilic cytoplasm were present in three cases. No papillary structures were noted. Hemorrhage (n = 21 tumors) (Fig. 2), a lymphoid infiltrate (n = 2 tumors), microcysts (n = 3 tumors), and necrosis (n = 2 tumors) also were noted. The background pancreatic parenchyma demonstrated fibrosis and focal lymphocytic infiltrate, consistent with chronic pancreatitis (n = 18 cases; only focal pancreatic parenchyma was present in the remaining three cases, too few to assess for any evidence of chronic pancreatitis). The lesional cells were separated from the ductal structures and from the islets, forming a distinct cell population, except for two cases in which there were multifocal microscopic deposits of tumor. A sarcomatous pattern was identified in two of the cases (Fig. 3), although the clear cell tumor pattern was the dominant feature.

Special procedures

The special techniques that were applied duplicated the usual findings expected for RCC. The metastatic foci contained variable amounts of glycogen in the cytoplasm of the clear cells that were accentuated by the PAS reaction and were removed with diastase treatment. The intensity varied from weak to strong, ranging from patchy (n = 4 cases) to diffuse (n = 13 cases) in distribution (no special stains were performed on four cases). No stainable mucin was demonstrated in the neoplastic cells in any of the cases that were tested.

Most of the metastatic foci were reactive with a variety of epithelial markers, including keratin (n = 11 cases), epithelial membrane antigen (n = 10 cases), CK7 (n = 9 cases), and CAM5.2 (n = 8 cases) (Table 5, Fig. 4). The tumor cells also were reactive with vimentin (n = 9 cases). Keratin immunoreactivity, as expected, was demonstrated in both the metastatic cells and the pancreatic ductal and centroacinar epithelial cells. There was a slight difference in the pattern of reactivity, with an accentuation along the cytoplasmic membranes in the metastatic RCC cells, with only a focal, granular, cytoplasmic reaction. The pattern of reactivity was diffuse and strong for the epithelial markers except for CK7, in which the staining was noted only focally but was distinct and intense. CA 19-9 was negative in the metastatic deposits, as expected, whereas it reacted appropriately in the cytoplasm of the ductal pancreatic parenchymal cells. CEA was negative in all of the metastatic foci. Proliferation markers p53 (n = 11 tumors) and Ki-67 (n = 8 tumors) were reactive (Fig. 4), with variable expression ranging

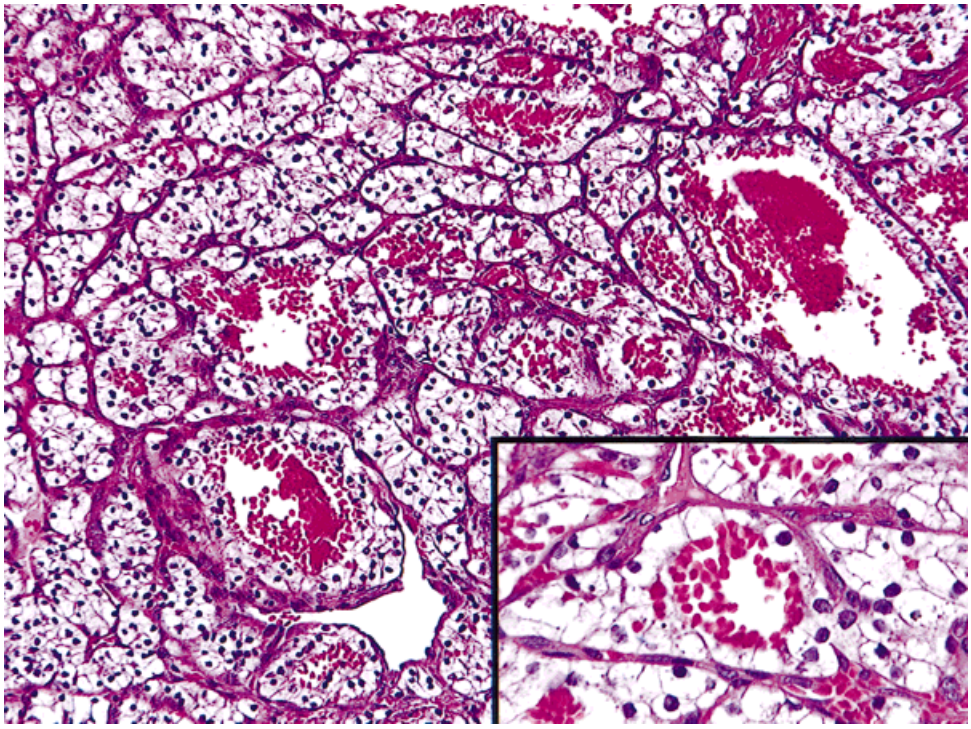

FIGURE 2. Clear cells of a metastatic renal cell carcinoma arranged in sinusoidal pattern with extravasated erythrocytes within the central regions. The inset demonstrates clear cytoplasm of cells with sharp, well-defined cellular borders. Nuclear atypia is minimal.

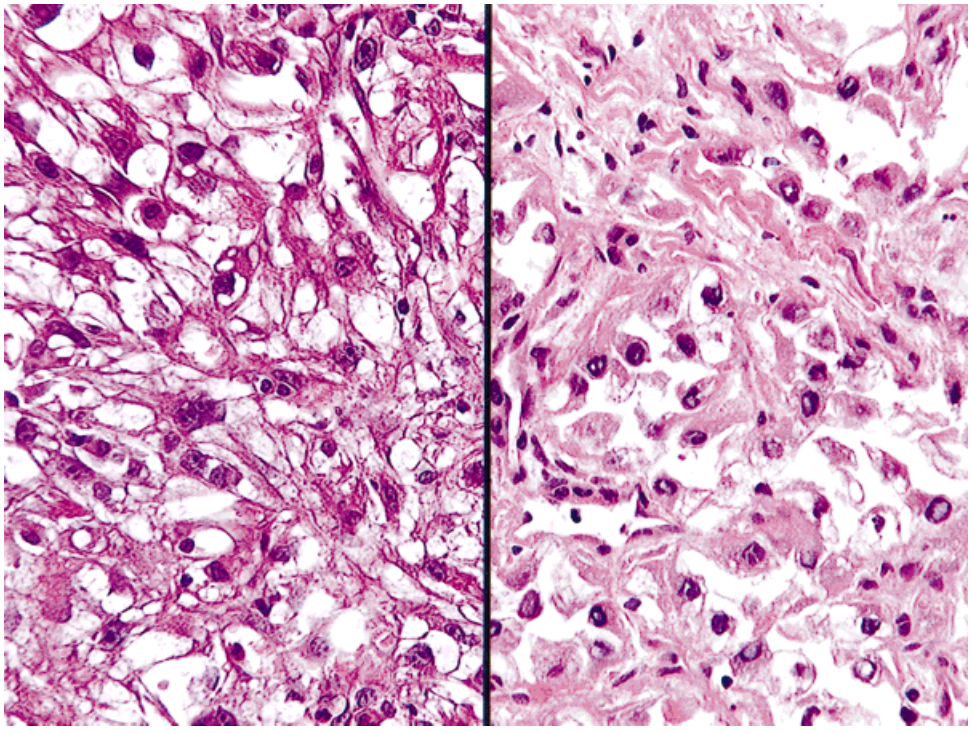

FIGURE 3. The left field demonstrates a sarcomatoid pattern of growth, whereas the right illustrates a "glandular" architecture of a metastatic renal cell carcinoma with cytologically atypical cells.

from <1% to >90% of the cells demonstrating strong reactivity. The antibody gp200 AB-1, which is a marker that is found in the distal tubule of the kidney, is known to react with cells of renal origin and was immunoreactive in 9 of 11 cases that were tested, usually accentuated along the membrane and lumen of the cells rather than diffusely in the cytoplasm. None of the pancreatic tissues reacted with this antibody.

Clinical Management and Outcome

All pancreatic masses were managed by surgery, irrespective of the treatment for the primary RCC. The

TABLE 5
Immunohistochemical Panel Results

Antibody	No. of patients with positive reactions (n = 13)
Cytokeratin (AE1/AE3 and CK1)	11
Cytokeratin 7	9 (F)
Cytokeratin 20	0
Epithelial membrane antigen	10
CAM 5.2	8
CA 19.9	0
CEA	0
Vimentin	9
Ki-67	6 (< 1%)
Ki-67	2 (< 10%)
p53	3 (< 1%)
p53	2 (< 10%)
p53	2 (25%)
p53	4 (< 90%)
gp200 Ab-1	9 of 11

F: focal reactivity noted in all cases with a positive reaction; CEA: carcinoembryonic antigen.

treatment included biopsy (n = 6 patients), distal pancreatectomy and splenectomy (n = 9 patients), partial pancreatectomy (n = 4 patients), or a Whipple procedure (n = 2 patients) (Table 6). Additional surgery or chemotherapy was employed as dictated by the completeness of the resection. In all of our patients, the pancreatic mass was an isolated clinical finding at the time of presentation, even though, during the follow-up period, other metastatic foci developed, specifically in the liver, spleen, adrenal gland, colon, stomach, kidney, and lymph nodes.

Follow-up was available for all patients (Table 7). All patients had clear cell RCC without any primary chromophobe or papillary RCC. Overall, 8 patients were either alive (n = 5 patients) or had died (n = 3 patients) without evidence of disease (mean, 9.0 years), whereas 13 patients had died with widely disseminated disease (mean, 4.5 years). These results yielded an overall raw 5-year survival rate of 42.9% and a raw 10-year survival rate of 23.8%. Because pancreatic metastases were already present, an RCC disease free survival rate is meaningless.

In an effort to simplify the follow-up data, the patients were grouped according to whether or not there was previous evidence of RCC (Table 7). In addition, survival from the date of the diagnosis of RCC is presented (Table 7).

Pancreatic Tumor as the Initial Presentation

In four patients (two men and two women), the pancreatic mass was the initial manifestation of the disease, promoting a clinical and radiographic investigation. A nephrectomy was performed between 2 months and 13.2 years after the diagnosis of a metastatic clear cell carcinoma to the pancreas, with radiographic images taken during the interim that did not demonstrate any primary tumor.

RCC as the Initial Presentation but with Subsequent Pancreatic Symptoms

Seventeen patients had been treated by a nephrectomy for RCC from 1 week to 32.7 years before the development of the pancreatic metastases (mean, 14.6 years) (Table 7). Overall, the mean survival was 5.2 years from the date of the pancreatic presentation and 19.8 years from the date of the diagnosis of RCC. At death, other metastatic foci included the liver, spleen, adrenal gland, lymph nodes, kidney, vertebrae, colon, stomach, lung, pleura, brain, and bones.

DISCUSSION

Metastasis to the pancreas is uncommon, although it has been described at autopsy in between 3% and 10% of patients with generalized malignancies,[37,39,40,47,55,60–64] nearly four times more common than primary tumors. When pancreatic invasion from carcinoma of adjacent organs (stomach, colon, ovary, gallbladder, and retroperitoneal sarcomas) and systemic malignancies (lymphoma and leukemia) are excluded, the truly metastatic tumors to the pancreas usually arise from lung, breast, skin (specifically melanoma), colon, stomach, ovary, or kidney.[1] Moreover, when clinical rather than autopsy series are reviewed, metastatic tumors comprise only about 3% of pancreatic tumors.[20,25,29,37,47,60,63] The scarcity of antemortem evidence of metastatic disease probably is related to the lack of symptoms or the nonspecific nature of the symptoms. The initial clinical symptoms include abdominal pain, weight loss, fatigue, malaise, anemia, diarrhea, bleeding, jaundice, and a mass lesion (Tables 2 and 3). Notably, the metastatic foci were discovered in 14–24% of our cases and those of the literature in patients who were asymptomatic. The foci were found incidentally during radiographic diagnostic surveillance studies that were performed during routine oncology follow-up for the primary RCC.

Intrapancreatic metastases can be identified by ultrasound, CT scan, MRI, and angiography. There are a number of radiologic studies that detail the findings of metastatic RCC to the pancreas and that may be of value in rendering a correct prebiopsy diagnosis.[5,6,11,24,25,29,30,38,44,48,65] The tumors can be solitary or multifocal, inhomogeneous masses, often containing hemorrhage or necrosis. Multifocal or multinodular disease suggests metastatic disease over a primary pancreatic disorder. The tumors are described as hypoechoic on ultrasound, occasionally demonstrating cystic degeneration.[5,6,11,48] The noncontrast CT scan

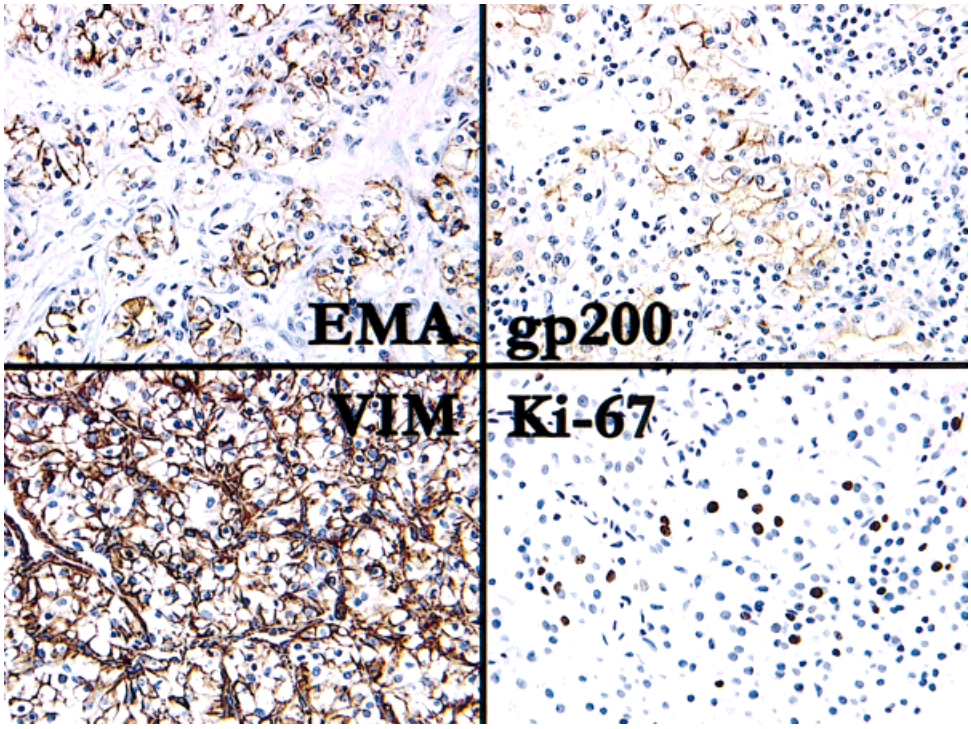

FIGURE 4. The immunophenotypic expression of metastatic renal cell carcinoma demonstrates epithelial membrane antigen (EMA), gp200, vimentin (VIM), and Ki-67 immunoreactivity, whereas it lacks immunoreactivity for CA19-9 and carcinoembryonic antigen.

TABLE 6
Patient Outcome Based on Treatment: Years of Follow-Up After the Pancreatic Presentation

Treatment	No. of patients	A, NED (yrs)	D, NED (yrs)	D, D (yrs)
All patients	21	5	3	13
Biopsy	1	n/a	n/a	1 (0.3)
Followed by surgery and/or chemotherapy	5	1 (19.8)	n/a	4 (1.1)
Distal pancreatectomy and splenectomy	5	3 (3.3)	1 (11.9)	1 (13.9)
Followed by surgery and/or chemotherapy	4	n/a	n/a	4 (3.8)
Partial pancreatectomy	1	n/a	1 (6.8)	n/a
Followed by surgery and/or chemotherapy	3	1 (1.9)	n/a2	(11.1)
Whipple procedure followed by surgery	2	n/a	1 (21.8)	1 (2.7)

A, NED: alive, no evidence of disease; D, NED: dead, no evidence of disease; D, D: dead, with disseminated disease; n/a: not applicable.

demonstrates a hyperattenuating mass, often with nonenhancing internal components—unlike primary pancreatic carcinoma. An intrapancreatic location of a metastatic deposit may cause biliary or pancreatic duct obstruction, making it difficult to separate a primary pancreatic tumor from a metastasis.[5,25,29,30,38] There usually is no retropancreatic fat obliteration. When it is present, the obliteration of the fat suggests a pancreatic primary tumor or direct continuity from the lymph nodes, as may be seen with a lymphoma.[6] Although they are nonspecific, the MRI features include diffuse enhancement for the small lesions, rim enhancement for larger lesions on immediate postgadolinium images, and a high signal intensity on T2-weighted images. Whereas these findings can be nonspecific, the "tumor blush" of a hypervascular RCC when using angiography can help to yield an accurate diagnosis, especially when there are no endocrine symptoms (circulating pancreatic hormones).[5,6,23,24,29,38,48]

RCCs are neoplasms of adulthood that are seen most frequently in the sixth decade of life with a male predominance. Similar to the literature (Table 2), a high proportion of the patients in our series of RCC metastatic to the pancreas were men. The average age of our patients at presentation (64.4 years) was similar to the findings reported in the literature (61.1 years) (Table 2). The primary tumor developed in the right and left kidney almost equally in the cases reported in the literature and in our cases. Bilateral primary tu-

TABLE 7
Patient Outcome Depending on Clinical Presentation

Outcome	A, NED (yrs)	D, NED (yrs)	D, D (yrs)
All patients (no.)	5	3	13
Survival *range* from date of pancreatic presentation	1.9–19.8	6.8–21.8	0.1–21.8
Survival *mean* from date of pancreatic presentation	6.3	13.5	4.5
Years between primary and metastatic disease (mean)	13.5	19.2	8.2
Survival from date of RCC diagnosis (mean)	19.8	32.8	13.5
RCC as initial presentation (no.)	5	2	10
Survival *range* from date of pancreatic presentation	1.9–19.8	6.8–11.9	0.1–13.9
Survival *mean* from date of pancreatic presentation	6.3	9.4	3.8
Years between primary and metastatic disease (mean)	13.5	28.9	12.1
Survival from date of RCC diagnosis (mean)	19.8	38.3	16.0
Pancreatic metastasis as initial presentation (no.)	0	1	3
Survival *range* from date of pancreatic presentation	n/a	n/a	0.7–21.8
Survival *mean* from date of pancreatic presentation	n/a	21.8	6.9
Years between primary and metastatic disease (mean)	n/a	−0.1	−5.1
Survival from date of RCC diagnosis (mean)	n/a	21.7	1.8

RCC: renal cell carcinoma; A, NED: alive, no evidence of disease; D, NED: dead, no evidence of disease; D, D: dead, with disseminated disease; n/a: not applicable.

mors giving rise to metastatic disease in the pancreas have been reported in the literature,[7,16,17,24,43,45,46,49] although we did not have any patients with bilateral tumors. The distinction between a metastasis to the contralateral kidney and a second primary tumor is beyond the scope of this discussion. Suffice it to say that bilateral RCC tumors, whether they are synchronous, metachronous, or metastatic, are possible theoretically and can give rise to pancreatic metastases.

RCC is known for its capacity to behave in an unpredictable and unusual fashion. Metastatic foci from RCC usually develop in the pulmonary system, skeletal system, lymph nodes, brain, liver, and skin, with other sites (such as the pancreas) described less frequently.[25,27,33,40,64,66,67] The recognition of metastatic foci in most tumors is important clinically, because metastases usually implies a poor prognosis, with the exception of a few tumors, such as RCC. It is peculiar that RCCs are known to develop late and/or solitary metastases. Although metastatic foci are present in about 25% of RCCs at the time of primary diagnosis (synchronous),[27,60,64,67–70] metastatic disease can develop as part of the latency of the tumor, with delayed development of metastases after many years of dormancy (metachronous), especially if the tumor is well-differentiated.[6,7,20,27,48,54,64,67,68,71,72] Moreover, a solitary metastasis from RCC occurs with an incidence rate of around 1–4%,[14,37,40,47,64,68,70,73,74] of which about 1–2% are recognized to occur in the pancreas. There are clearly many tumor cells in the peripheral circulation, although only a few form metastases, suggesting that a solitary RCC metastasis implies the ability of the host to destroy the majority of the cells.[71] Although it was not proven in this study, it is possible that the pancreas provides an immunologic haven that allows for the slow development of tumor growth and specifically for metastatic RCC. Further study is needed to identify why the pancreas and pulmonary systems harbor solitary metastatic deposits more frequently than other organs.

Metastatic RCC may be the first manifestation of the disease, even masquerading as a primary pancreatic neoplasm. In the setting of a solitary pancreatic mass many years after nephrectomy in a patient with a long disease free interval (arbitrarily defined as >10 years[27]), the recognition that it may be an RCC may pose a diagnostic problem not only for the pathologist but also for the clinician. The absence of symptoms related to the urinary tract in many cases and sometimes a failure to obtain a detailed clinical history may lead to an equivocal or incorrect diagnosis when the patient first presents with a pancreatic mass.

In none of the patients in our series was the RCC discovered simultaneously with the metastatic pancreatic tumor. Given the nature of our consultation service, the history of RCC usually was disclosed within a few days of rendering the opinion. It is interesting to note that, in four of our cases, the metastatic focus was the initial presentation of the RCC, and, in one case, it took 13.2 years before the primary RCC finally was removed. However, on average, the metastatic focus developed 14.6 years after the initial nephrectomy (range, 1 month to 32.7 years). Twelve patients presented 10 years or more after the initial nephrectomy. These results are only slightly different from those presented in the literature, in which it is reported that 16 patients presented simultaneously, and the average duration between the nephrectomy and the pancreatic metastasis was 11.1 years (range, 6 months to 27 years).

Surgical treatment of patients with solitary pancreatic metastases is recommended because of the unusually good prognosis of our patients as well as those reported in the literature (Table 2) when they were treated with definitive surgical therapy. A few factors may be associated with this favorable prognosis after resection of such metastases, including 1) a long interval between the primary tumor resection and the development of the metastatic focus (often in excess of 10 years), 2) evidence of a solitary or isolated lesion in the pancreas (usually identified radiographically), 3) spontaneous regression of metastatic lesions, 4) demonstration of extensive necrosis in the resected specimen, and 5) slow evolution or growth of the tumor and a lack of clinical symptoms.[7,13,35,37,39,42,47,57,64,66,68,71,75] Moreover, the spontaneous remission or regression of cancer metastases are uncommon but have been well described in RCC and especially in RCC metastases to the lung.[66,71,76,77] There is only a single case report of spontaneous regression of an RCC metastatic to the pancreas.[1] None of the patients in our series had a spontaneous regression, but all had surgery within a short time of the documentation of the metastasis rather than only being followed clinically.

The mean survival reported in the literature is 1.3 years after the metastatic focus was resected (Table 2), ranging from a few days to 6 years. However, the data on patient survival in a case report or small series with a short follow-up period are not necessarily reliable for the purpose of predicting survival. It has been suggested that, in the setting of solitary RCC metastasis (any anatomic site), the 5-year survival rate from the date of the nephrectomy is between 30% and 70%,[27,57,64,67,68,70,74] much higher than the approximately 5% 5-year survival rate when widespread disease is present.[27,37,47] In our series, the 5-year survival rate from the date of nephrectomy was 81%, and the 10-year survival rate was 76%. In fact, the mean overall survival from the date of the nephrectomy was 19.8 years (range, 0.7–39.6 years), with a 6.2-year mean overall survival from the date of the pancreatic metastasis (range, 1 month to 21.8 years) (Table 7). Therefore, there is an overall excellent prognosis for RCC patients with solitary metastases (disease stage was not reported for the original material), further highlighting the necessity for surgical resection of solitary metastatic foci to the pancreas to assure a good clinical outcome.

The preoperative distinction between a primary and secondary pancreatic neoplasm is almost impossible, and the metastatic nature of the tumor can be recognized only after tumor sampling. Therefore, all patients for whom there is clinical or radiographic evidence of a mass (particularly in solitary masses) in the pancreas, and especially those patients for whom surgery has been performed previously for malignant growth elsewhere (not just a renal cell tumor), need to have the lesion biopsied. If the previous known primary tumor is of kidney derivation, then the suspicious radiographic lesion should be resected rather than biopsied, because this may provide for a better clinical outcome. However, if the previous malignancy is of an unknown primary origin, then the biopsy technique can include fine-needle aspiration (FNA) of the pancreas (percutaneous or with endoscopy), which may provide an accurate diagnosis,[6,8,10,18,32,55] allowing for the institution of proper treatment and possibly allowing a better long term survival to be achieved. If FNA cannot be used, then open biopsy and resection are suggested. The challenge of making the diagnosis of a metastatic clear cell RCC in the pancreas on frozen section is difficult due to fixation artifacts that make the cytoplasm appear more eosinophilic than clear. However, the architecture may help in making an accurate distinction between a primary tumor and a metastatic tumor.

The tumors in our series seemed to involve the body and tail (33%) slightly more frequently than other sites (Table 4), but involvement of the head was nearly as common (29%). Diffuse, multifocal involvement occurred in 19% of our cases. Although the data are more difficult to interpret from the literature, 33% of the reported cases occurred in the body, body and tail, and tail, whereas 41% developed in the head. Nearly 15% involved the pancreas diffusely (Table 2). The differences are not sufficiently different to suggest a notable predilection for a particular part of the pancreas.

The tumors presented in the pancreas as either a solitary mass (52%) or as multifocal nodules (43%). The type of presentation was difficult to assess in the literature; however, when it was reported, it seemed to present as a solitary mass more frequently (71%).

Pancreatic metastases from RCC can mimic primary pancreatic neoplasms, including serous cystadenoma, clear cell adenocarcinoma, islet cell tumor, or sugar tumor.[3] RCC and clear cell primary tumors of the pancreas may show a morphologic overlap, making a distinction between these tumors difficult if not impossible without additional information or studies. This distinction is complicated further by the identification of sarcomatous transformation in the RCC metastatic focus, which was described in two of our cases and in the literature.[17,58]

The distinction between a metastatic RCC and a microcystic adenoma of the pancreas sometimes is fraught with difficulty. This difficulty may be accentuated further in patients with von Hippel–Lindau disease, an inherited chromosomal-dominant disease

that manifests both RCC (25%) and pancreatic cysts (simple cysts or microcystic adenoma; up to 75%), among other disorders within the syndrome.[9,49,78] None of our patients declared the stigmata of von Hippel–Lindau disease clinically. Furthermore, the literature does not include the use of any special stains or immunophenotypic studies to prove whether the patients with von Hippel–Lindau disease actually had RCC metastatic to the pancreas or whether the pancreatic lesion may have been a microcystic adenoma.[9,49,78,79] Radiographically, a microcystic adenoma usually is composed of a grape-like cluster of innumerable cysts frequently arranged around a central, stellate scar. Histologically, both lesions can have small, gland-like structures and a low nuclear to cytoplasmic ratio with clear cytoplasm surrounding nonatypical, hyperchromatic nuclei. A rich vascular pattern can be seen in both tumors.[80] However, RCC tends to form a sheet of cells separated by thin, fibrovascular septa with a sinusoidal vascular pattern with hemorrhage into the glandular lumina. The microcystic adenoma tends to have fibrotic bands separating cells that are arranged around a larger "cyst-like" lumen. PAS positive, diastase sensitive glycogen also is found in both lesions. The immunophenotypic expression may help to distinguish between these lesions, in which CA 19-9 is reactive in pancreatic ductal tumors,[81] and gp200 and milk fat globulin are reactive only in metastatic RCCs. However, these tests cannot always discriminate completely and reproducibly between the tumors. Radiographic and clinical correlation must be implemented to define fully the nature of the tumor.

Clear cell adenocarcinoma of the pancreas has abundant, clear cytoplasm surrounding atypical nuclei, similar to metastatic RCC. RCCs usually are arranged in glands, short cords, or trabeculae separated by a prominent vascular stroma. The cells of RCC have clear cytoplasm, distinct boundaries, and small, compact, hyperchromatic nuclei, which may or may not be atypical. The distinction of pancreatic clear cell adenocarcinoma from metastatic RCC can be assisted by an intense, positive, oil-red O reaction and strong vimentin, CK7, and gp200 immunoreactivity within the RCC cells accompanied by a negative mucin stain and nonreactive CK20, CEA, and CA 19-9.[63,81–84]

A rare islet cell tumor can present with clear cells but usually is positive with chromogranin and a variety of different peptide hormones that are specific to the islets of Langerhans. Chromogranin is not reactive in RCC, although serotonin has been reported to be reactive.[3,62,63] A sugar tumor of the pancreas is extremely unusual. Although the sinusoidal pattern is present, the tumor cells are reactive with HMB-45 and are negative for keratin.[85]

Immunohistochemical studies may help to distinguish between metastatic tumors and primary tumors of the pancreas. CEA and CK20 are reported to be positive in pancreatic adenocarcinomas in 80–90% of patients, whereas they are nonreactive in patients with RCC, and CK7 is reactive in most patients with RCC and not in patients with pancreatic neoplasms.[83,84] The antibody gp200 is a newly defined antibody that seems to react in RCC, although we did not identify any reactivity in the few pancreatic clear cell tumors that we tested (microcystic adenomas and mucinous cystadenocarcinomas of low grade malignant potential). Finally, vimentin usually is identified in RCC ($> 90\%$), whereas very few pancreatic carcinomas react with vimentin ($< 10\%$).[83]

Although a genetic analysis was not performed in any of the cases in this series or in the literature, it is well known that a k-*ras* mutation at codon 12 occurs in $> 90\%$ of human pancreatic ductal adenocarcinomas, including clear cell carcinoma of the pancreas.[84,86] This same k-*ras* mutation has been described in only $< 6\%$ of patients with RCC.[87]

In summary, the identification of a clear cell tumor of the pancreas must be worked up to exclude the possibility of metastatic RCC, especially when it is found in a patient with a previous history of RCC, no matter how long ago the nephrectomy was performed. Although the clinical manifestations and radiographic findings may be nonspecific, histochemical and immunohistochemical studies may help in the distinction whether they are performed on FNA material or surgical biopsies. Surgical treatment of the metastatic disease is suggested, because the patient still may have a prolonged survival, especially if the RCC was known before the metastasis, as proven in these and other reported cases.

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