The Dermatologist's Guide to Hereditary Syndromes With Renal Tumors

Pascal G. Ferzli, MD; Christian R. Millett, MD; Marissa D. Newman, MD; Warren R. Heymann, MD

GOAL

To understand the cutaneous manifestations of 4 hereditary syndromes with renal tumors to better manage patients with these conditions

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the most common cutaneous features of 4 hereditary syndromes with renal tumors.
2. Discuss the association between cutaneous findings and the risk of renal cancer.
3. Identify appropriate screening tests for patients with cutaneous findings.

CME Test on page 70.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: December 2007.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Drs. Ferzli, Millett, Newman, and Heymann report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

Patients with hereditary syndromes with renal tumors initially may present to the dermatologist. It is essential that dermatologists recognize these syndromes because the early diagnosis of renal cancer may prove to be lifesaving. The 4 hereditary syndromes with cutaneous manifestations are von Hippel-Lindau (VHL) syndrome, Birt-Hogg-Dube (BHD) syndrome, tuberous sclerosis (TS), and hereditary leiomyoma renal cell carcinoma (HLRCC) syndrome. This article reviews these disorders, emphasizing their cutaneous features and renal manifestations.

Cutis. 2008;81:41-48.

Accepted for publication April 18, 2007.

Dr. Ferzli is a dermatology resident, Dr. Millett is a medicine intern, and Dr. Heymann is Head, all from the Division of Dermatology, Department of Medicine, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Camden. Dr. Newman is a medicine intern, North Shore University Hospital, Manhasset, New York.

Correspondence: Warren R. Heymann, MD, Cooper Hospital, Department of Dermatology, 3 Cooper Plaza, Suite 215, Camden, NJ 08103 (heymanwr@umdnj.edu).

Dermatologists have a unique opportunity to recognize hereditary syndromes associated with renal tumors. By doing so, it may be possible to diagnose these tumors before they become life threatening. Although these syndromes are rare, it is incumbent upon dermatologists to recognize these disorders and recommend appropriate screening tests and referral to other specialists,

Hereditary Renal Cancers

Syndrome	Chromosome Locus (Gene Product)	Predominant Renal Tumor Type	Associated Abnormalities
von Hippel-Lindau*	3p25-26 (*VHL*)	Clear cell carcinoma	Retinal hemangioblastomas, pancreatic cysts, neuroendocrine tumors of pancreas, pheochromocytoma
Tuberous sclerosis*	9q34 (hamartin), 16p13.3 (tuberin)	Clear cell carcinoma	Cortical tubera, cardiac rhabdomyomas, facial angiofibromas
Hereditary papillary renal cancer	7q34 (hepatocyte growth factor receptor)	Papillary cell carcinoma type 1	None
Hereditary leiomyoma renal cell carcinoma*	1q42.3-43 (fumarate hydratase)	Papillary cell carcinoma type 2	Cutaneous and uterine leiomyomas
Birt-Hogg-Dube*	17p11.2 (folliculin)	Chromophobe carcinoma	Fibrofolliculomas, pneumothorax, lung cysts
Hereditary renal oncocytoma	Unknown	Oncocytoma	Renal dysfunction
Translocation from chromosome 3	To chromosome 2, 6, 8, 11	Clear cell carcinoma	None
Lynch syndrome type II	2p16 *(MSH)*, 3p31 *(MLH1)*	Transitional cell carcinoma of renal pelvis	Cancer of colon, endometrium, ovaries, stomach
Medullary carcinoma of the kidney	11p	Medullary carcinoma	Sickle cell trait

*Cutaneous manifestations.

Adapted with permission from Choyke et al.[2]

including urologists, oncologists, and geneticists. Of the 9 known hereditary syndromes with renal tumors, 4 demonstrate cutaneous manifestations: von Hippel-Lindau (VHL) syndrome, Birt-Hogg-Dube (BHD) syndrome, tuberous sclerosis (TS), and hereditary leiomyoma renal cell carcinoma (HLRCC) syndrome.

Renal cell carcinoma (RCC) is diagnosed in more than 30,000 individuals in the United States each year, causes 12,000 deaths annually, and is increasing in incidence.[1] Known risk factors for sporadic renal cancer include smoking, chemical exposure, asbestosis, obesity, hypertension, and end-stage renal disease. There is growing recognition that heredity also plays a role, and it is estimated that approximately 4% of renal cancers are hereditary. In these individuals, a germ line mutation is associated with a predisposition to develop renal tumors of specific histologic types.[2]

In the past 10 years, advances in genomics and the widespread use of modern imaging techniques have contributed to the awareness of hereditary renal cancer syndromes. Increased knowledge of these syndromes will allow dermatologists to screen

and counsel family members as well as identify those patients at risk for multiple cancer development. Early screening to identify localized tumors will provide opportunities to therapeutically intervene while cancers are still treatable.[3] Because 4 of these syndromes involve cutaneous manifestations, the dermatologist may have the opportunity to make the diagnosis at an early stage.

Hereditary renal cancers differ from sporadic renal cancers in several important respects.[2] A hallmark of hereditary renal cancer is that tumors often are multiple and bilateral. Unlike sporadic renal cancers, which develop in the sixth and seventh decades of life, hereditary renal cancers may develop much earlier, even in teenaged individuals. Although sporadic renal tumors are more common in men, hereditary renal cancers often are found with equal frequency in both sexes. Disease severity can be highly variable, even within a family, and the absence of a family history never completely excludes the possibility of a hereditary cause for renal cancer.[2]

Renal Tumor Classification

There are several histologic types of renal cancer in adults and each is linked with a specific hereditary syndrome.[2] The most common histologic subtype is clear cell carcinoma, which accounts for 75% of renal cancers. Clear cell carcinomas arise from the proximal tubular epithelium. Grossly, they appear yellow because of their high lipid content. Microscopically, these cells appear lucent because of their high glycogen content. Clear cell carcinomas are seen in VHL syndrome and TS.[2]

The second most common type of renal cancer is papillary cell carcinoma (15%).[4] It is subclassified into type 1 and type 2. Type 1 is found in hereditary papillary renal cancer and is associated with a good long-term prognosis. It is characterized by cells with scant pale cytoplasm arranged in a single layer. Type 2 is found in HLRCC syndrome and is a more aggressive form. Type 2 cells are pseudostratified with an eosinophilic cytoplasm.[4]

Chromophobe carcinoma is the third most common cell type.[3] This tumor contains cells with well-defined borders, large eosinophilic cytoplasm, and pyknotic nuclei with a perinuclear halo. The cell of origin is most likely the intercalated cell of the cortical collecting duct. Chromophobe carcinomas account for approximately 5% of renal cancers and are found in BHD syndrome.[3]

Oncocytomas account for 2% to 3% of renal tumors and are considered to be benign renal neoplasms.[5] Grossly, they are mahogany brown and are not necrotic. Histologically, they are composed of tightly packed tubular structures or nesting cells surrounded by a reticulin skeleton. They commonly grow centrifugally from a central avascular scar. Oncocytomas can be found in BHD syndrome and hereditary renal oncocytoma.[5]

Rare malignant tumors of the kidney include collecting duct and medullary carcinomas, which represent only 1% of renal tumors. Transitional cell carcinoma of the renal pelvis is another cause of malignancy in the kidneys and is associated with hereditary nonpolyposis colon cancer syndrome (Lynch syndrome).[6] A common benign tumor of the renal parenchyma is angiomyolipoma, which is a hamartoma of the kidneys that contains vascular, lipomatous, and myeloid elements. Most of these tumors are small and slow growing. The primary risk associated with angiomyolipoma is hemorrhage. These tumors are found in TS.[7] The Table lists the hereditary renal cancers and their respective chromosomal and clinical associations.

Clinical Manifestations of Renal Tumors

Because of their insidious course and varied clinical presentations, renal tumors most commonly are diagnosed as incidental findings during radiologic procedures.[8] The classic triad of symptoms—hematuria, flank pain, and an abdominal mass—is seen only in approximately 10% of patients; in most cases, only one of these symptoms is the initial manifestation of the tumor. Systemic symptoms may be present, including weight loss, fatigue, and fever. RCC also is associated with several paraneoplastic syndromes, such as polycythemia (from ectopic erythropoietin production) and hypercalcemia (from ectopic production of parathyroid hormone–related peptide). Metastases mainly are through hematologic spread, and the lungs, bones, and liver are the most frequent sites.[8]

Prognosis and Staging of Renal Tumors

RCC remains a major source of morbidity and mortality.[9] Approximately 40% of patients eventually die of cancer progression, making RCC the most lethal of the common urologic malignancies. Although modern imaging has led to earlier diagnosis of RCC, more than 20% of patients present with metastatic disease. Tumor stage remains the most important prognostic factor for RCC. When renal cancers are organ confined, the 5-year survival rate is between 74% and 96%. This rate decreases to 40% to 60% when the renal veins are involved. With locally advanced renal cancers, as well as those with lymphatic involvement or metastasis, the 5-year survival rate is 0% to 20%.[9]

Treatment of Renal Tumors

Surgical resection (nephrectomy, partial nephrectomy) remains the most viable treatment option for RCC, regardless of the stage of disease at presentation. For localized tumors, surgical cure of disease is strongly dependent on stage and grade of disease.[10] For locally advanced or metastatic disease, nephrectomy should be considered for palliation or as part of an adjuvant therapy protocol. Curative lymphadenectomy is not possible in most cases, and the value of lymphadenectomy is limited to those patients with lymph node involvement. Limited dissection of tissue and resection of the visible or palpable nodes usually is sufficient.[11]

Renal tumors respond poorly to radiation, chemotherapy, and immunotherapy, with response rates of less than 20%.[12] However, advances in the understanding of immune responses to RCC have led to new therapeutic strategies based on immune manipulation. The identification of numerous T-cell epitopes associated with RCC has led to the development of new treatment approaches using DNA vaccination, peptide vaccination, and dendritic cell therapy; combined with new and more efficient gene-delivery techniques, these treatments may have considerable clinical implications for patients with RCC.[12] Targeted therapies that are currently being investigated for metastatic RCC include tyrosine kinase inhibitors (ie, sorafenib), anti–vascular endothelial growth factor therapy (ie, bevacizumab), and inhibition of the mammalian target of rapamycin (mTOR) pathway (ie, temsirolimus).[13]

VHL Syndrome

VHL syndrome represents a constellation of central nervous system (CNS) and visceral neoplasms that result from a germ line mutation of the *VHL* tumor suppressor gene on chromosome arm 3p25-26.[14] In this autosomal dominant neurocutaneous syndrome, 80% of cases are hereditary and 20% are sporadic. The incidence of VHL syndrome is approximately 1 in 36,000 individuals.[15] Patients with VHL syndrome typically present before the age of 40 years.[16] Although less than 5% of cases of VHL syndrome have dermatologic manifestations, capillary malformations are the most common cutaneous features. Thus, the dermatologist must be vigilant to observe for VHL syndrome in the appropriate clinical context.

More than 70% of sporadic clear cell RCCs display mutations in the *VHL* gene.[17] The *VHL* protein produced via this gene is a ubiquitin ligase that degrades hypoxia-inducible factors (HIFs) including HIF-1α and HIF-2α. A mutation of the *VHL* gene can increase the levels of HIF, which subsequently activate additional genes that produce vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor α, and carbonic anhydrase IX. In concert, these factors facilitate neoangiogenesis and tumorigenesis.[17]

The mutation of the *VHL* gene leads to the development of both benign and malignant tumors that affect multiple organ systems. CNS tumors include retinal hemangioblastomas (20%–60%); endolymphatic sac tumors (11%–16%); and craniospinal hemangiomas, most frequently of the cerebellum (44%–72%), brainstem (10%–25%), and spinal cord (13%–50%). Additional manifestations of VHL syndrome include RCC or kidney cyst (25%–60%), epididymal cystadenoma (25%–60% of men), pancreatic cyst or cystadenoma (17%–56%), pheochromocytoma or paraganglioma (10%–20%), and broad ligament cystadenoma (10% of women).[18] The capillary malformations of VHL syndrome often occur in but are not limited to the head and neck. Also, café au lait spots that frequently are associated with neurofibromatosis may be evident in VHL syndrome, suggesting overlap between these phakomatoses.[19] VHL syndrome is a progressive disease, with death characteristically occurring by the fourth decade of life.

The diagnosis of VHL syndrome is based on clinical criteria. Patients with a family history of VHL syndrome and a CNS hemangioblastoma, pheochromocytoma, or clear cell RCC are diagnosed with the syndrome. In the absence of a family history, the diagnosis can be made with 2 or more CNS hemangioblastomas and a visceral tumor, with the exclusion of renal and epididymal cysts. Confirmation of diagnosis and screening for possibly affected family members can be achieved with DNA testing for mutation in the *VHL* gene. Recommended laboratory tests include a complete blood count and screenings for serum catecholamine and urine vanillylmandelic acid levels, as well as a computed tomographic scan (CT scan) and/or magnetic resonance imaging of the brain, spinal cord, and abdomen.

Patients diagnosed with VHL syndrome should be referred to an ophthalmologist for photocoagulation or cryocoagulation of tumors. Neurosurgeons and urologists may surgically remove CNS and renal tumors, respectively, with preoperative angiography. Patients with VHL syndrome also may consider renal transplantation.

BHD Syndrome

BHD syndrome, an autosomal dominant genodermatosis occurring in 1 in 200,000 individuals, is

characterized by the cutaneous triad of fibrofolliculomas, trichodiscomas, and acrochordons. Vincent and colleagues[20] offer a comprehensive analysis of these papules, which frequently appear in the third to fourth decades of life. Protein-truncating mutations of the *BHD* gene on chromosome arm 17p11.2 encode the *BHD* protein folliculin, which is expressed in the kidneys, lungs, and skin.[21] Although the function of the protein is unknown, the *BHD* gene is presumptively involved in tumor suppression.

Fibrofolliculomas and trichodiscomas are clinically indistinguishable; both are skin-colored, well-circumscribed, smooth, firm, 2- to 4-mm papules distributed over the forehead, nose, and cheeks.[22] Acrochordons appear as soft pedunculated lesions. The clinical appearance of fibrofolliculomas and trichodiscomas is associated with familial spontaneous pneumothorax and RCCs. Notably, patients with BHD syndrome have a 50-fold increased risk of pneumothorax presenting with tachypnea, decreased breath sounds, and hyperresonance.[23] Lung cysts and bullous emphysema also have been associated with BHD syndrome. In addition to the cutaneous and pulmonary features, a 7-fold increase in renal tumors with varying histology has been associated with BHD syndrome, including hybrid chromophobe and oncocytoma (50%), chromophobe (34%), clear cell RCC (9%), and oncocytoma (5%).[23] Multiple histologic types can be found in the same family, patient, and kidney, suggesting a role for the *BHD* gene in the differentiation processes of renal cells.

Fibrofolliculomas possess a circumscribed fibrous tissue layer around the hair follicles.[24] These follicles demonstrate a widened infundibulum containing laminated keratin. Encasing the follicle is a mantle of loose connective tissue embedded in a mucoid ground substance with high concentrations of hyaluronic acid. The elastin fibers may not be visible or appear sparse. Radiating from the follicular epithelium are 2 to 4 thin layers of epithelial strands that extend into the fibrous tissue where they combine with epithelial strands or connect with follicular or sebaceous epithelium. In contrast, the histology of the trichodiscomas demonstrates hair follicles at the margin of these tumors. The stroma is highly vascularized, with collagen fibers and cells containing melanin.[24]

A diagnosis of BHD syndrome requires 5 or more facial or truncal papules; 1 papule must be confirmed as a fibrofolliculoma or trichodiscoma using the histologic criteria above. The differential diagnosis includes TS, Cowden syndrome, Brooke-Spiegler syndrome, Rombo syndrome, and basaloid follicular hamartoma syndrome. It is recommended that all patients who are diagnosed with BHD syndrome get a chest x-ray, abdominal CT scan, and renal ultrasound. Thereafter, patients may be screened every 3 to 5 years. Siblings of patients require physical examinations and biopsies of suspicious skin lesions as early as the second decade of life.

Treatment options for fibrofolliculomas and trichodiscomas include CO_2 laser ablation and/or erbium:YAG laser, copper vapor laser, and systemic isotretinoin, though these therapies have shown variable results in some patients.[24] Resection is recommended for RCC. If the tumor is less than 3 cm in size, surgery that conserves the parenchyma may be appropriate to optimize renal function without increasing the risk of metastases. The prognosis depends on the renal and pulmonary sequelae.

Tuberous Sclerosis

TS, also called tuberous sclerosis complex (TSC), is a rare genetic disease that causes benign tumors to grow in the brain and other organs, such as the kidneys, lungs, skin, and eyes.[25] Its incidence is 1 in 10,000 individuals and the age of presentation is variable.

TS is an autosomal dominant disorder; approximately 40% of cases are hereditary and 60% are sporadic.[26] Two gene mutations have been identified in contributing to the development of TS: the hamartin gene *TSC1* on the chromosome arm 9q34 and tuberin gene *TSC2* on the chromosome arm 16p13.3. The latter is adjacent to the *PKD1* site, which is responsible for autosomal dominant polycystic kidney disease, thereby explaining the association of these 2 disorders in patients with contiguous gene defects. Hamartin and tuberin associate in vivo to form a tumor suppressor complex. This complex functions within the P13K-Akt-mTOR pathway and regulates nutrient and growth factor signaling to mTOR. As a result, rapamycin has potential therapeutic use in TS.[26]

The clinical features of TS include neurologic involvement with mental cognitive deficiency and epilepsy; psychiatric and behavioral problems such as attention deficit hyperactivity disorder and generalized development delays; and organic brain anomalies such as cortical tubera, subependymal giant cell astrocytomas, and subependymal nodules.[25] Cardiac rhabdomyomas, retinal hamartomas, and dental pits also are typical findings of TS. Pulmonary lymphangioleiomyomatosis related to TS has been described, usually presenting exclusively in women. Classic cutaneous lesions include facial angiofibromas (adenoma sebaceum), the

shagreen patch, and periungual or subungual fibromas (Koenen tumors).[25]

Renal manifestations are mainly angiomyolipomas, renal cysts, and cancer.[27] In patients with TS, multiple lesions appear concomitantly and are likely to be bilateral. Larger lesions may present with flank pain, hypertension, hematuria, and renal failure. These lesions characteristically are benign, though there are some reports of sarcomatous degeneration and rare malignant epithelioid variants.[27]

Angiomyolipomas are not hamartomas per se, rather they are clonal perivascular epithelioid cell tumors (PEComas).[28] PEComas are tumors composed of mostly epithelioid cells positive for HMB-45 and/or melan-A as well as actin- and/or desmin-positive cells. These PEComas have a perivascular propensity. They belong to a family of mesenchymal neoplasms that include angiomyolipomas, lymphangioleiomyomatosis, clear cell tumor (sugar tumor) of the lung, and other soft tissue and visceral neoplasms with similar histology and immunohistochemistry. Pan et al[29] studied the cytogenetic feature of these tumors and reported that all cells studied had gross chromosomal anomalies, with the most frequent being a deletion of chromosome arm 16p, in which *TSC2* is located. Alam et al[30] concluded that PEComas are distinctive tumors based on the common chromosomal changes found in both renal and extrarenal tumors.

Starting in childhood, renal ultrasounds can be used to detect and monitor the growth of angiomyolipomas. Because complications correlate with increasing size, surgery is recommended when the tumor is greater than 3.5 to 4.0 cm in size. Surgical options include tumor embolization, tumor enucleation, partial nephrectomy, or total nephrectomy depending on the presentation. Patients with TS are at a higher risk for renal cancer than the general population (2.0%–4.0% vs 1.27%, respectively) and are more likely to present at a younger age (30 years vs 60 years, respectively). Renal cancer in patients with TS is most commonly of the clear cell carcinoma type and is more likely to be multifocal and bilateral.[2] For these reasons, lifelong periodic radiologic evaluation is essential.

HLRCC Syndrome

HLRCC syndrome is an autosomal dominant disease that is an expansion of Reed syndrome (multiple cutaneous and uterine leiomyoma syndrome). It is characterized by the presence of leiomyomas in the skin and uterus of affected females and in the skin of affected males. Its prevalence in the general population is not known, though one limited study estimated the presence of a heterozygous fumarate hydratase, *FH*, gene mutation at 1 in 676 individuals.[30]

Germ line mutations in the *FH* gene at chromosome arm 1q42.3-43 are associated with the HLRCC syndrome.[31] In the Krebs cycle, the *FH* and succinate dehydrogenase, *SD*, genes act as tumor suppressors. Mutations in the *SD* gene are associated with pheochromocytomas and paragangliomas. Mutations in the *FH* gene lead to the overexpression of HIF-1α and its targets (eg, vascular endothelial growth factor), which contributes to tumorigenesis by the so-called pseudohypoxic drive. There is a low frequency of *FH* mutations in sporadic cases of leiomyomas and leiomyosarcomas.[31]

The clinical features of patients with HLRCC syndrome include benign cutaneous and uterine leiomyomas and, more rarely, cutaneous leiomyosarcomas and uterine leiomyosarcomas. Cutaneous leiomyomas usually present in late childhood to early adulthood. They typically present as multiple disseminated lesions, most commonly on the face, trunk, and extremities, though segmental distribution also has been described.[30] The individual lesions appear as intradermal papules. Alam et al[30] stated that 90% of patients complain of pain from cutaneous leiomyoma, which is exacerbated by cold or trauma.

Although leiomyomas may be solitary and sporadic lesions, Chuang et al[32] noted that the finding of a cutaneous leiomyoma in a patient should compel dermatologists to examine the individual and his/her family for multiple lesions and to screen for the *FH* gene, which is crucial because *FH* mutations in HLRCC syndrome lead to increased susceptibility to early-onset RCC. These RCCs usually are solitary, fast growing, and very aggressive, and they display papillary cell carcinoma type 2 or renal collecting duct histology. Alam et al[30] reported a case of a 16-year-old patient who presented with metastatic renal disease, which led the authors to urge the consideration of early screenings for *FH* mutations for patients.

Toro et al[33] screened 35 families with cutaneous leiomyomas for mutations in the *FH* gene. They identified mutations in 31 families (89%). Eighty-one individuals had cutaneous leiomyomas, of which 47 were women and 34 were men. Forty-six of 47 women (98%) had uterine leiomyomas. The authors also found 13 individuals in 5 families with unilateral and solitary renal tumors. Seven individuals from 4 families had papillary cell

carcinoma type 2, and 1 individual from 1 of these families had renal collecting duct carcinoma.[33]

Patients who present with lesions that are diagnosed as cutaneous leiomyomas should prompt a complete history, including a history of fibroids in women as well as a family history of fibroids or renal tumors.[34] Tests for mutations in the *FH* gene may be of value. Renal imaging studies should be performed in suspect cases. Although some papillary cell carcinoma type 2 or collecting duct RCCs can be found only with a CT scan or magnetic resonance imaging, a simple ultrasound is successful in most cases and can sometimes provide superior information about the characteristics of the renal tumor.[34]

Conclusion

Dermatologists have a unique opportunity to diagnose hereditary renal tumors before they become life threatening. When examining patients with capillary malformations, fibrofolliculomas, angiofibromas, or leiomyomas, the dermatologist should consider the possibility of VHL syndrome, BHD syndrome, TS, or HLRCC syndrome, respectively. With a positive family history, renal imaging studies should be obtained. Although these syndromes are rare, it is essential that dermatologists recognize them for the benefit of the patients and their kin.

REFERENCES

1. Pavlovich CP, Schmidt LS, Phillips JL. The genetic basis of renal cell carcinoma. *Urol Clin North Am*. 2003;30:437-454, vii.
2. Choyke PL, Glenn GM, Walther MM, et al. Hereditary renal cancers. *Radiology*. 2003;226:33-46.
3. Schmidt LS. Birt-Hogg-Dube syndrome, a genodermatosis that increases risk for renal carcinoma. *Curr Mol Med*. 2004;4:877-885.
4. Hes O, Brunelli M, Michal M, et al. Oncocytic papillary renal cell carcinoma: a clinicopathologic, immunohistochemical, ultrastructural, and interphase cytogenetic study of 12 cases. *Ann Diagn Pathol*. 2006;10:133-139.
5. Amin MB, Crotty TB, Tickoo SK, et al. Renal oncocytoma: a reappraisal of morphologic features with clinicopathologic findings in 80 cases [published correction appears in *Am J Surg Pathol*. 1997;21:742]. *Am J Surg Pathol*. 1997;21:1-12.
6. Greenland JE, Weston PM, Wallace DM. Familial transitional cell carcinoma and the Lynch syndrome II. *Br J Urol*. 1993;72:177-180.
7. O'Hagan AR, Ellsworth R, Secic M, et al. Renal manifestations of tuberous sclerosis complex. *Clin Pediatr (Phila)*. 1996;35:483-489.
8. Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*. 22nd ed. Philadelphia, PA: WB Saunders & Co; 2004.
9. Kontak JA, Campbell SC. Prognostic factors in renal cell carcinoma. *Urol Clin North Am*. 2003;30:467-480.
10. Hutson TE. Renal cell carcinoma: diagnosis and treatment, 1994-2003. *Proc (Bayl Univ Med Cent)*. 2005;18:337-340.
11. El-Galley R. Surgical management of renal tumors. *Radiol Clin North Am*. 2003;41:1053-1065, vii.
12. Michael A, Pandha HS. Renal-cell carcinoma: tumour markers, T-cell epitopes, and potential for new therapies. *Lancet Oncol*. 2003;4:215-223.
13. Patel PH, Chaganti RS, Motzer RJ. Targeted therapy for metastatic renal cell carcinoma. *Br J Cancer*. 2006;94:614-619.
14. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260:1317-1320.
15. Neumann HP, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. *Lancet*. 1991;337:1052-1054.
16. Maher ER, Iselius L, Yates JR, et al. von Hippel-Lindau disease: a genetic study. *J Med Genet*. 1991;28:443-447.
17. Linehan WM, Vasselli J, Srinivasan R, et al. Genetic basis of cancer of the kidney: disease-specific approaches to therapy. *Clin Cancer Res*. 2004;10(18, pt 2):6282S-6289S.
18. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. *Lancet*. 2003;361:2059-2067.
19. Horton WA, Wong V, Eldridge R. von Hippel-Lindau disease: clinical and pathological manifestations in nine families with 50 affected members. *Arch Intern Med*. 1976;136:769-777.
20. Vincent A, Farley M, Chan E, et al. Birt-Hogg-Dube syndrome: a review of the literature and the differential diagnosis of firm facial papules. *J Am Acad Dermatol*. 2003;49:698-705.
21. da Silva NF, Gentle D, Hesson LB, et al. Analysis of the Birt-Hogg-Dubé (BHD) tumour suppressor gene in sporadic renal cell carcinoma and colorectal cancer. *J Med Genet*. 2003;40:820-824.
22. Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. *Am J Hum Genet*. 2005;76:1023-1033. Epub April 25, 2005.
23. Zbar B, Alvord WG, Glenn G, et al. Risk or renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002;11:393-400.
24. Welsch MJ, Krunic A, Medenica MM. Birt-Hogg-Dubé syndrome. *Int J Dermatol*. 2005;44:668-673.
25. Clinical features of tuberous sclerosis complex. Children's Hospital of St. Louis Web site. http://www.stlouischildrens.org/tabid/91/itemid/3705/Clinical-Features-of-Tuberous-Sclerosis-Complex.aspx. Accessed September 20, 2006.

26. Kwiatkowski DJ, Manning BD. Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. *Hum Mol Genet*. 2005;14 spec no. 2:R251-R258.
27. Kawaguchi K, Oda Y, Nakanishi K, et al. Malignant transformation of renal angiomyolipoma: a case report. *Am J Surg Pathol*. 2002;26:523-529.
28. Hornick JL, Fletcher CD. PEComa: what do we know so far? *Histopathology*. 2006;48:75-82.
29. Pan CC, Jong YJ, Chai CY, et al. Comparative genomic hybridization study of perivascular epithelioid cell tumor: molecular genetic evidence of perivascular epithelioid cell tumor as a distinctive neoplasm. *Hum Pathol*. 2006;37:606-612.
30. Alam NA, Barclay E, Rowan AJ, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. *Arch Dermatol*. 2005;141:199-206.
31. Heymann WR. Cutaneous manifestations of hereditary syndromes. *J Am Acad Dermatol*. 2006;54:505-506.
32. Chuang GS, Martinez-Mir A, Engler DE, et al. Multiple cutaneous and uterine leiomyomata resulting from missense mutations in the fumarate hydratase gene. *Clin Exp Dermatol*. 2006;31:118-121.
33. Toro JR, Nickerson ML, Wei MH, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. *Am J Hum Genet*. 2003;73:95-106. Epub May 22, 2003.
34. Hélénon O, Correas JM, Balleyguier C, et al. Ultrasound of renal tumors. *Eur Radiol*. 2001;11:1890-1901.