Nonneoplastic Kidney Diseases in Adult Tumor Nephrectomy and Nephroureterectomy Specimens

Common, Harmful, Yet Underappreciated

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• Context.—Nonneoplastic kidney diseases, such as arteriosclerosis and/or diabetic nephropathy, are commonly encountered in tumor nephrectomy and nephroureterectomy specimens. Although any nonneoplastic kidney disease may be encountered in these resection specimens by chance, additional diseases that may be related to the underlying neoplasm or its treatment regimen include thrombotic microangiopathy, Amyloid A amyloidosis, membranous nephropathy, immunoglobulin A nephropathy, membranoproliferative glomerulonephritis, pauci-immune crescentic glomerulonephritis, focal segmental glomerulosclerosis, minimal-change disease, acute interstitial nephritis, and xanthogranulomatous pyelonephritis. Given the morbidity of chronic kidney disease and the relatively favorable 5-year survival rates for urothelial and renal cell carcinomas, accurate evaluation of the nonneoplastic kidney parenchyma is important.

Objectives.—We will discuss our approach for evaluating the nonneoplastic kidney parenchyma in tumor nephrectomy and nephroureterectomy specimens. The pathologic features of the aforementioned kidney diseases as well as pertinent references will be reviewed. The identification of glomerular abnormalities, including mesangial sclerosis or hypercellularity, segmental sclerosis, crescent formation, glomerulitis, or glomerular basement membrane alterations, should lead to additional immunofluorescence and electron microscopic studies. Safeguards to ensure that the nonneoplastic parenchyma is not overlooked include adding this important parameter to synoptic reports and obtaining periodic acid–Schiff and/or Jones methenamine silver stains prior to microscopic evaluation of the neoplasm.

Data Sources.—Relevant literature and University of Chicago Medical Center pathology archives.

Conclusions.—The practicing surgical pathologist should be aware of the importance of both correctly classifying the resected renal or urothelial neoplasm and the concomitant nonneoplastic kidney disease that may be present in these specimens.

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The current evaluation of tumor nephrectomy and nephroureterectomy specimens centers around the pathologic diagnosis, grade, and stage of the neoplasm. The application of synoptic reporting based on protocols and checklists from either the College of American Pathologists or the Association of Directors of Anatomic and Surgical Pathology serves to minimize the risk of missing any important pathologic parameters.1,2 However, the assessment of the nonneoplastic kidney parenchyma is not a required parameter in either protocol, and concomitant nonneoplastic renal lesions are often overlooked during the pathologic assessment of these specimens.3 In this review we will redirect the attention of the surgical pathologist to this important component.

Chronic kidney disease (CKD), previously known as chronic renal failure, is common and affects 1 in 9 adult patients, or roughly 20 million people in the United States.4 Approximately 500,000 Americans have end-stage renal disease (ESRD), requiring renal replacement therapy (renal transplantation or dialysis), which cost $32 billion in 2004.5 The risks for both cardiovascular and noncardiovascular deaths are elevated in CKD patients, who typically die before progressing to ESRD. Of interest, up to 25% of renal cell carcinoma (RCC) patients have CKD prior to nephrectomy, and those with normal renal function are more likely to develop CKD after a radical nephrectomy procedure.6,7 The substantial reduction of functional nephrons after partial or radical nephrectomy is often compounded by the concurrent effects of hypertension and diabetes, which are both important risk factors for developing RCC,10–14 as well as CKD and, subsequently, ESRD. Therefore, it is not surprising that medical renal diseases are found in up to 60% of adult tumor nephrectomy specimens, of which most are attributed to diabetes or hypertension.15

Renal cell carcinoma comprises 2% to 3% of all adult malignancies.16 With continuing advances in imaging, surgical techniques, and therapeutic regimens, renal neoplasms are detected earlier with improving survival rates, which will lead to more cures and longer periods free of
disease or recurrence. Although radical nephrectomy is the usual surgical treatment of RCC, nephron-sparing resections are more commonplace, as the preservation of renal function becomes an important consideration for the clinical outcome and quality of life in RCC survivors. The average 5-year survival rate for RCC patients is greater than 90%, 75% to 90%, and 59% to 70% for those with stages I, II, and III disease, respectively. Similar survival rates are observed in patients with urothelial carcinomas of the upper urinary tract. According to the 2004 US Renal Data System, the average 60-, 70-, or 80-year-old with ESRD on dialysis has a life expectancy of 4.3, 3.1, or 2.2 years, respectively, which is substantially lower than the life expectancy of any RCC patient with stage I, II, or III disease. A patient having both ESRD and stage I, II, or III urothelial or RCC would be more likely to die of his or her kidney disease than the underlying malignancy. These data underscore the significant morbidity of both CKD and ESRD.

Surgical pathologists have an opportunity during the evaluation of tumor nephrectomy and nephroureterectomy specimens to identify a variety of medical renal diseases. Similar to cancer, early detection of such lesions provides the best opportunity to intervene with appropriate therapies and to delay the progression of kidney injury. In fact, the evaluation of the nonneoplastic renal parenchyma becomes the most important determinant of clinical outcome when a benign renal or urothelial neoplasm is encountered. Based on the initial light microscopic examination, most renal diseases can be identified or suspected, which should prompt additional immunofluorescence (IF) and/or electron microscopy (EM). The surgical pathologist should adopt a systematic approach when evaluating the nonneoplastic renal parenchyma and be familiar with the characteristic histopathologic features of nonneoplastic renal diseases that commonly occur in nephrectomy and nephroureterectomy specimens.

**A PRACTICAL AND SYSTEMATIC APPROACH**

Given that the best practices for the evaluation of the nonneoplastic renal parenchyma in tumor nephrectomy and nephroureterectomy specimens have not been established, we will provide our approach for evaluating this important component. Proper examination includes a systematic inspection of all 4 anatomic compartments of the kidney—the glomeruli, tubules, interstitium, and vessels, and requires the assistance of periodic acid–Schiff (PAS) and/or Jones methenamine silver (JMS) stains. To optimize visualization of the glomeruli and glomerular basement membranes (GBMs), these tissue sections should be 2 μm in thickness rather than the 3- to 4-μm–thick sections that are typical of general surgical pathology specimens. To minimize the possibility of missing renal lesions, we suggest that the special stains should be available when the hematoxylin-eosin–stained sections of the neoplasm are being reviewed.

In general, the evaluation of well-preserved and nonischemic glomeruli will be more informative, which should not be limited to a small number of glomeruli, because many glomerular lesions can be quite focal. If glomerular alterations, such as crescents, fibrinoid necrosis, GBM abnormalities (eg, thickening, “spike” formation, or double contours), mesangial sclerosis or mesangial hypercellularity (>2 mesangial cells per mesangial region away from the vascular pole in a 2-μm–thick section), infiltrations by inflammatory cells, or endocapillary proliferation, are present, direct IF and/or EM should be performed using formalin-fixed, paraffin-embedded tissue, albeit with generally less sensitivity for IF microscopy and processing/preservation artifact for EM. When direct IF microscopy is performed on the paraffin tissue sections, we routinely stain for immunoglobulin (Ig) G, IgA, IgM, κ and λ light chains, and albumin. In our laboratory, IF staining of paraffin sections for the complement components, C3c and C1q, has not been useful, but this contrasts with the experience of others. Immunohistochemistry for immunoglobulins and complement components is another technique that can be performed on paraffin tissue sections and has been more widely used in Europe.

The vascular compartment should be examined for the presence of intimal fibrosis, fibrinoid necrosis or vasculitis, intraluminal thrombi, athereombi, or hyalinosis. The tubulointerstitial compartment will demonstrate various degrees of interstitial fibrosis and tubular atrophy that may correlate with the degree of arteriosclerosis. Histologic features of acute tubular injury (or acute tubular necrosis) may be present, but the diagnosis should be made with caution, because this may represent a preservation artifact and is a finding of uncertain clinical significance in the setting of nephrectomy. Generally, mild interstitial inflammatory mononuclear cell infiltrates often accompany areas of interstitial fibrosis and tubular atrophy and are considered nonspecific findings. When a prominent interstitial inflammatory infiltrate is present between well-preserved tubules with interstitial edema and tubulitis (lymphocytes present between the tubular basement membrane and tubular epithelial cells), this warrants the diagnostic consideration of acute interstitial nephritis. Rare cases of concurrent non-Hodgkin lymphoma have been reported (see below).

Evaluation of the nonneoplastic renal parenchyma immediately adjacent to the neoplasm should be avoided when possible. Depending on the size of the renal neoplasm, the immediate 3 to 5 mm of adjacent renal parenchyma may demonstrate secondary changes from compression by the tumor. Partial nephrectomy specimens may not provide the most representative sample of the nonneoplastic renal parenchyma. Despite this limitation, diagnostic findings within these suboptimal areas, including prominent vascular or glomerular abnormalities, such as nodular glomerulosclerosis, may still be identifiable.

For optimal results, direct IF microscopy should be performed on a sample of nonneoplastic renal parenchyma frozen in optimal cutting temperature compound and EM studies using tissue preserved in glutaraldehyde or paraformaldehyde-based fixatives. However, saving such samples for potential IF and EM studies on all tumor nephrectomy or nephroureterectomy specimens would be quite time consuming and costly. From a practical perspective, another approach would be to reserve a portion of nonneoplastic renal parenchyma in appropriate fixatives for future IF and EM studies only if a clinical suspicion for a glomerular disease (proteinuria or hematuria with red blood cell casts) is known when grossing the specimen. In the only prospective study on this topic, additional IF and EM testing was performed on saved tissue in only 10 of 60 tumor nephrectomy specimens (16.7%), which resulted in 5 additional diagnoses (8.3%; 2 IgA nephropathy cases with mild IgA deposition detected by IF; 2 cases of thin GBM disease, and 1 case of renal immunoglobulin light...
States. Approximately one third of diabetic patients will develop diabetic nephropathy (DN), which is associated with high morbidity and mortality. Diabetes is an established risk factor for developing RCC and is present in approximately 10% to 20% of RCC patients. Pathologic features of DN are seen in up to 20% of tumor nephrectomy specimens.

Diabetic nephropathy demonstrates a constellation of histopathologic changes affecting all 4 anatomic compartments of the kidney. Initially, the glomeruli become enlarged. Diffuse thickening of both the tubular and glomerular basement membranes gradually develops. Diffuse mesangial matrix deposition (or sclerosis) is found in varying degrees of severity and may be difficult to identify in the early stages (Figure 1, A). More advanced cases develop nodular mesangial sclerosis (or nodular glomerulosclerosis), also known as Kimmelstiel-Wilson nodules (Figure 1, B). These acellular nodules may reveal layering or a lamellated appearance. Mesangiolysis (dissolution and fraying of the matrix) with aneurysmal dilatation of the glomerular capillaries also may be present. Sometimes, mesangial nodules and aneurysmal dilatation of the capillaries can still be appreciated within globally sclerotic glomeruli using the PAS or JMS stains. Additional characteristic features of DN are hyalinosis or insudative lesions (fibrin caps and capsular drops) that represent localized collections of plasma proteins. Fibrin caps represent accumulations of hyaline within glomerular capillaries that may obliterate the lumen. Capsular drops are accumulations of similar hyaline material between the glomerular capillaries and Bowman capsule. The hyaline is PAS positive with a homogeneous staining quality that has a staining intensity similar to that of the GBM. This hyaline can also be present within the arterioles in a subendothelial location, which may be segmental or circumferential. Vascular disease may be advanced and widespread in DN. Intimal fibrosis is often observed in the larger arteries. Characteristic subendothelial hyalinosis involves both the afferent and efferent glomerular arterioles, but the appropriate tissue section through the vascular pole to visualize both arterioles is uncommon. Immunofluorescence microscopy typically demonstrates generally weak linear staining of the glomerular and tubular basement membranes, with similar intensities for both IgG and albumin, but this staining pattern is not specific.
for DN and also can be seen in the setting of hypertension and renal allografts. The EM features of DN are nonspecific and should confirm the light microscopic features, such as thickening of the GBM and increased mesangial matrix deposition. Occasionally, this matrix can have a vague fibrillar appearance, which has been termed diabetic fibrilosis and should not be mistaken for the fibrils of amyloid (10–12 nm in thickness) or fibrillary (roughly 20 nm in thickness) glomerulonephritis (GN). There is no single histopathologic feature that is pathognomonic for DN, but the constellation of the aforementioned features is highly suggestive of this important and common diagnostic entity.

Although nodular glomerulosclerosis (or nodular mesangial sclerosis) is a characteristic feature for DN, this finding is not specific and should provoke consideration of other entities, including renal amyloidosis, monoclonal immunoglobulin deposition disease, fibrillary GN, and immunotactoid glomerulopathy. A Congo red stain is used to help establish the diagnosis of renal amyloidosis, and the other entities can be diagnosed with the aid of IF and/or EM. Also, cases of idiopathic nodular glomerulosclerosis in association with hypertension and smoking have been reported in patients without diabetes.30,31 Therefore, the pathologic diagnosis of DN should never be made without first establishing or confirming the clinical diagnosis of diabetes.

Bijol et al32 found that nodular glomerulosclerosis (defined in their study as containing prominent Kimmelstiel-Wilson nodules) in tumor nephrectomy specimens was predictive of significantly decreased renal function within 6 months after surgery. Strict blood glucose control is the mainstay of therapy for both type 1 and type 2 diabetes. Long-term normoglycemia can halt the progression of DN, and possibly reverse the process of mesangial expansion.32 Thus, diagnosing DN at any stage is important so that preventive measures or proper therapy can be administered.

**ARTERIONEPHROSCLEROSIS**

Arterionephrosclerosis (also called hypertensive nephropathy/nephrosclerosis) is the most common finding in adult tumor nephrectomy specimens. The term benign has been used to qualify this entity, but it should be avoided because this injury process can be quite harmful and frequently leads to ESRD. We prefer using the descriptive term of arterionephrosclerosis because the clinical history of hypertension may not always be available at the time of pathologic evaluation.

Hypertension affects roughly 25% of the US adult population and is the second most common cause of ESRD in the United States.27 Depending on the study, 25% to 60% of RCC patients are hypertensive.6,26,33 Bijol et al15 reported that 37% of nephrectomy specimens demonstrated mild to severe arterial and arteriolar sclerosis with minimal parenchymal changes, and an additional 22% of specimens demonstrated more severe vascular changes with parenchymal scarring. The pathologic diagnosis of arterionephrosclerosis is based on a constellation of nonspecific histopathologic features. The gross appearance of the kidney shows granularity of the capsular surface, which corresponds to the light microscopic glomerular and tubulointerstitial scarring due to this vascular injury. Additional light microscopic features include proliferative and fibrotic intimal thickening with narrowing of the arteries that may be accompanied by replication of the internal elastic lamina. Subendothelial hyalinosis affecting primarily the afferent but not efferent glomerular arterioles is often observed. Early glomerular changes are initiated by ischemic injury to the glomerulus with thickening and wrinkling of the basement membranes, usually in a global distribution along with thickening and fraying of Bowman capsule (Figure 2, A). Collagen gradually accumulates in the urinary space and compresses the shrunken glomerular tufts until eventually the entire glomerulus is sclerotic (Figure 2, B). Globally sclerotic glomeruli (global glomerulosclerosis) may be arranged in wedge-shaped zones of chronic ischemic injury of the outer cortex if the blood flow of larger renal arteries is compromised (Figure 2, C). Global glomerulosclerosis is associated frequently with tubular atrophy and interstitial fibrosis of the surrounding parenchyma because the blood exiting the efferent glomerular arteriole supplies the adjacent peritubular capillaries. Progressively more glomeruli are involved until the process results in ESRD with few residual intact nephrons. In advanced arterionephrosclerosis, there may be glomerular enlargement and superimposed focal segmental glomerulosclerosis, which has been postulated to be secondary to overloading the decreasing numbers of functional nephrons.

There are no pathognomonic histopathologic features for arterionephrosclerosis. In the absence of an immune complex–mediated injury, the combination of global glomerulosclerosis, interstitial fibrosis and tubular atrophy, and arteriosclerosis is consistent with this diagnosis. Given that global glomerulosclerosis involving more than 20% of glomeruli is predictive of worsening of renal function 6 months after nephrectomy,15 an estimated percentage of global glomerulosclerosis is an important feature to report.

**THROMBOTIC MICROANGIOPATHY**

Thrombotic microangiopathy (TMA) with predominantly chronic features is found in up to 5% of tumor nephrectomy specimens.15 Typical clinical signs include microangiopathic hemolytic anemia and thrombocytopenia. The pathologic finding of TMA can occur in a number of clinical settings, including but not limited to thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, scleroderma, preeclampsia, antiphospholipid antibody syndrome, radiation nephritis, drug toxicity, and disseminated intravascular coagulation. Thrombotic microangiopathy also has been associated with a variety of malignancies, including RCC.34,35 Correlation with the clinical history is necessary to establish the correct etiology of TMA.

In the acute phase of TMA, fibrin thrombi may be observed within glomerular capillaries and extraglomerular vessels. The affected vascular structure often has a distended appearance, which is a subtle feature that may be useful to distinguish from capillaries that are simply congested by red blood cells. Red blood cell fragments (erythrocytolysis) may be present within the intima of affected arterioles or arteries. A Masson trichrome stain can highlight the thrombi in bright red. An immunohistochemical stain for CD61, a platelet marker, can also be used to confirm the presence of these thrombi. Glomerular capillaries may appear bloodless because of prominent swelling of the endothelial cells and obliteration of the lumina. Mesangiolysis as well as capillary aneurysm formation may
Figure 2. Arterionephrosclerosis. A, This ischemic glomerulus shows shrinkage of the glomerular tufts and wrinkling of the glomerular basement membrane with perihilar accumulation of collagen. Some glomerular capillaries are no longer patent, but this should not be mistaken for segmental sclerosis (periodic acid–Schiff, original magnification ×400). B, Collagenization of the urinary space may be present in advanced stages of global glomerulosclerosis (periodic acid–Schiff, original magnification ×400). C, Global glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis in a wedge-shaped distribution with a slight depression of the capsular surface (top) corresponds with the macroscopic granular appearance characteristic of arterionephrosclerosis (hematoxylin-eosin, original magnification ×40).

Figure 3. Chronic thrombotic microangiopathy. Duplication of the glomerular basement membranes (arrows) without capillary or arteriolar thrombi or immune complex deposition (periodic acid–Schiff, original magnification ×600).

be present. As the endothelial cell injury persists, the glomerular capillary walls become thickened by expansion of the subendothelial zone, eventually resulting in duplication (or double contours) of the GBMs in the chronic phase of TMA, which is best seen with PAS and JMS stains (Figure 3). Arterioles demonstrate subendothelial expansion and thrombosis, which eventually progress to sclerotic lesions. A characteristic arterial lesion is mucoid intimal change. Prominent concentric intimal and smooth muscle cell hyperplasia of the arterioles or arteries (onion skinning) may also be present. Immunofluorescence microscopy can show staining for fibrinogen in thrombi, as well as nonspecific trapping of IgM and the complement components in involved glomerular capillaries and arteriolar vessel walls. Electron microscopy findings include subendothelial space widening of the endothelial cells and separation from the underlying GBM in acute injury, with duplication of the GBMs as a sign of chronicity.

The therapeutic regimen that is used frequently to treat RCC deserves further discussion. Most chemotherapeutic agents, including mitomycin C, gemcitabine, vincristine, doxorubicin, cyclophosphamide, cisplatin, and daunorubicin, have been associated with TMA. In addition, recently developed pharmacologic agents used to treat RCC include inhibitors of vascular endothelial growth factor, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor. These targeted inhibitors have improved survival rates for patients with cancer of the colon, lung, and breast, and are promising therapies for the treatment of advanced RCC. Sunitinib and sorafenib are oral multireceptor tyrosine kinase inhibitors that act on vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-KIT. Their side effects on the kidney include a preeclampsia-like syndrome with hypertension and proteinuria and acute in-
terstitial nephritis. In addition, therapy with bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, has been reported to cause TMA, Temsirolimus, an inhibitor of mammalian target of rapamycin, is another potential pharmacologic agent for treating RCC. This class of agents acts on the mammalian target of rapamycin pathway and has been widely used in the transplantation setting, primarily with sirolimus (rapamycin). Kidney injury with TMA or intra-tubular casts that may represent myoglobin have been reported with sirolimus, but such injuries have yet to be described with temsirolimus. Careful evaluation of the nonneoplastic kidney parenchyma serves the alternate purpose of establishing a baseline prior to the use of these potentially nephrotoxic agents that typically are given after nephrectomy. Also, metastatic RCC may call for the neoadjuvant administration of these agents prior to surgery. With the expanding use of targeted inhibitors against RCC, surgical pathologists should be familiar with the features of TMA when evaluating the nonneoplastic kidney parenchyma.

**SICKLE CELL NEPHROPATHY**

Although sickle cell disease is an uncommon cause of TMA, sickle cell nephropathy is worthy of additional attention given the association of renal medullary carcinoma with sickle cell trait and disease. In patients with sickle cell disease, the gross examination of the renal medulla may show congestion of the vasa recta in the renal medulla. In advanced disease, the vasa recta may be reduced in number, and papillary necrosis may be present. Careful histologic examination may reveal sickled red blood cells within the arteries and glomerular capillaries. The presence of prominent hemosiderosis in the proximal tubular epithelial cells is characteristic of this injury, which can be confirmed with a Prussian blue iron stain. Iron deposition may also be present in glomerular visceral and parietal epithelial cells. Focal global or segmental glomerular scarring can be seen. Chronic TMA with a membranoproliferative pattern of injury is common, and collapsing glomerulopathy with prominence of visceral epithelial cells has also been reported. Electron microscopy findings include fibrillary inclusions within the sickled red blood cells that represent polymerized hemoglobin.

**ATHEROEMBOLIC DISEASE**

Atheroembolic disease has been reported in up to 2% of tumor nephrectomy specimens and often occurs in patients with severe atherosclerotic disease. When the kidneys are involved, this disease can present with acute kidney injury or renal insufficiency. Atheroemboli may result spontaneously or as a complication of invasive vascular procedures. Light microscopy demonstrates cholesterol clefts within the lumen of affected vessels, which can range from glomerular capillaries to interlobular arteries and, rarely, large arcuate arteries. An acute lesion often has blood, fibrin, and perhaps multinucleated giant cells surrounding the cholesterol clefts, whereas a chronic atheroembolus is embedded within intimal proliferation and/or sclerosis. There is no specific therapy for atheroembolic disease, but it may explain any clinical presentation of renal insufficiency or acute kidney injury.

**AMYLOIDOSIS**

Renal amyloidosis affects approximately 3% of RCC patients. Although typically observed with chronic inflammatory states, such as rheumatoid arthritis or ankylosing spondylitis, more than 40 reported cases of AA amyloidosis are associated with RCC and demonstrate systemic involvement. This differs from endocrine tumors, such as medullary thyroid carcinoma and pancreatic islet cell tumors, where the non-AA amyloid deposits are limited to the involved organ. Renal cell carcinoma is the most common epithelial tumor, comprising 30% of carcinomas associated with AA amyloidosis. AA amyloidoses associated with urothelial carcinomas of the renal pelvis and bladder have also been reported. Other amyloid cases associated with RCC include AL amyloidosis and leukocyte chemotactic factor 2, and an angiomyolipoma with an uncharacterized protein. Renal amyloidosis is characterized by the deposition of amorphous eosinophilic material within glomeruli and/or vessel walls. A range of glomerular injury can occur, including nodular glomerulosclerosis. When visualizing with the PAS stain, the deposits stain less pink compared with the adjacent GBMs. The Congo red stain confirms the presence of amyloid deposits, which stain red and show green birefringence under polarized light. Positive staining for serum amyloid A protein by immunohistochemistry confirms the diagnosis of AA amyloidosis. Immunofluorescence studies may identify monoclonal amyloid deposits for either κ or λ light chain, which would be diagnostic of AL amyloidosis. Randomly arranged fibrils measuring 10 to 12 nm in thickness are observed by EM (Figure 4, D); they are thinner than the fibrils of fibrillary GN (approximately 20 nm). The pathogenesis of RCC-associated AA amyloidosis is not well understood, but a relationship with the underlying renal neoplasm is implicated. Removal of the renal neoplasm generally leads to resolution of both proteinuria and hepatic and splenic deposition of amyloid, but the glomerular deposits of amyloid may persist. Recurrence of proteinuria could indicate the presence of recurrent or metastatic RCC.

**MEMBRANOUS NEPHROPATHY**

Membranous nephropathy, also known as membranous glomerulopathy or membranous GN, is a common cause of adult-onset nephrotic syndrome. Approximately 10% of MN cases are associated with malignancy, which are typically carcinomas of the lung, gastrointestinal tract, and breast. Of all immune complex–mediated glomerular injuries that have been reported in carcinoma patients, MN is the most frequently observed, but only 10 RCC-associated MN cases have been reported in the English literature. The spectrum of glomerular injury in MN depends primarily on the extent of subepithelial immune complex deposition. Although cancer-associated MN has similar histopathologic features to idiopathic or primary MN, Lefaucheur et al recently found that the majority of cancer-associated MNs were in the early stages of development, and many demonstrated increased leukocytes within the glomerular capillaries, which has been termed glomerulitis or glomerular capillaritis. This histologic finding is an indication for additional IF and EM studies. Fewer than 10% of these cases also demonstrated glomerular microthrombi.
or TMA, but RCC-associated MN was not identified in this study. At an early stage of MN, the glomeruli appear normal by light microscopy, and even PAS or JMS stains may not demonstrate any apparent GBM abnormalities. At more advanced stages, prominent thickening of GBMs with perpendicular projections of basement membrane material or subepithelial “spikes” separating immune complexes can be visualized with PAS and JMS stains (Figure 5, A). When sectioned en face, the GBM may demonstrate vacuolizations imparting a “Swiss cheese” appearance. To determine whether the GBM is thickened, the tubular basement membrane of a well-preserved tubule can be used as a reference point, but this should be done with caution because both the tubular and glomerular basement membranes may undergo pathologic thickening in diabetes and hypertension. Varying degrees of segmental and/or global glomerular scarring (glomerulosclerosis) may be present. Immunofluorescent staining for IgG (Figure 5, B), and often C3, reveals granular deposits along the glomerular capillary walls. Cancer-associated MN cases may demonstrate more intense IF staining for IgG1 and IgG2, compared with more prominent IgG4 staining seen in idiopathic MN cases. By EM, subepithelial electron-dense deposits will be seen with or without intervening basement membrane material or spikes, and the overlying podocytes show extensive foot process effacement (Figure 5, C).

The pathogenesis of cancer-associated MN is unclear, but the glomerular injury may be mediated by immune complexes composed of tumor-associated antigens. Alternatively, malignancies can cause defects in immune regulation, and they may render the cancer patient more susceptible to the induction of antibodies against endogenous or exogenous antigens and the subsequent development of immune complex nephritis.

The resolution of proteinuria after surgical resection alone has been reported for both nonrenal carcinomas and RCC, which suggests a causal relationship with MN. In one of these reports, nephrotic syndrome recurred and correlated with the presence of metastatic disease.

**IgA NEPHROPATHY**

IgA nephropathy is the most common primary GN worldwide, including in the United States. IgA nephropathy—Henriksen et al
Figure 5. Membranous nephropathy. A, Prominent thickening of the glomerular basement membranes with focal subepithelial spike formation (arrow) is present (Jones methenamine silver, original magnification ×600). B, Granular direct immunofluorescent immunoglobulin G staining of the capillary walls was observed in the paraffin tissue sections (original magnification ×400). C, Electron microscopy shows diagnostic subepithelial electron dense deposits (arrows) with extensive foot process effacement of the overlying podocytes (original magnification ×3600).

Figure 6. Immunoglobulin A (IgA) nephropathy. A, Mild mesangial hypercellularity is more notable in the right half of this glomerulus (periodic acid–Schiff, original magnification ×600). B, Granular mesangial staining for IgA by direct immunofluorescence (IF) microscopy (original magnification ×200). C, Electron microscopy shows discrete, mesangial, electron-dense deposits (arrows), which confirms the IgA IF staining (original magnification ×2950).
Membranoproliferative glomerulonephritis (MPGN) is a well-known manifestation of hepatitis C. In the setting of malignancies, MPGN is often associated with non-Hodgkin lymphoma and is less commonly observed with solid tumors, with isolated reports associated with carcinoma of the breast, lung, stomach, prostate, bladder, and, only rarely, kidney. Membranoproliferative glomerulonephritis has also been reported in pediatric Wilms tumors. Membranoproliferative glomerulonephritis is characterized by the accentuation of the lobular architecture of the glomerular tufts and duplication of the GBMs (Figure 7). Immune complexes confirmed by IF and EM are present in primarily subendothelial and mesangial areas, with occasional subepithelial deposits. To our knowledge, dense deposit disease (also known as MPGN type II) has only been reported after immunosuppressive chemotherapy for breast carcinoma, not RCC. The pathogenesis of MPGN in the setting of malignancy is not understood and potentially may be related to tumor-associated antigens.

PAUCI-IMMUNE CRESCENTIC GN

Pauci-immune necrotizing and crescentic GN has been described in association with malignancies, including lymphoma, carcinoma of the stomach, lung, bladder and prostate, RCC, and after administration of immunotherapy for RCC. Necrotizing and crescentic GN has also been reported in association with on-
cyclophosphamide, which further underscores the importance of careful examination of the nonneoplastic kidney with this otherwise benign renal neoplasm. In a large study of Wegener granulomatosis, the most common malignancy was RCC in 7 patients (1.5%), of whom 5 had concurrent crescentic GN. In contrast, larger systematic studies of non-tumor kidney parenchyma have not identified pauci-immune crescentic GN. Lesions are characterized by fibrinoid necrosis of glomerular tufts with proliferation of epithelial cells resulting in crescent formation (Figure 8). Periodic acid–Schiff or JMS stains may reveal gaps in the GBM. Prominent tubulointerstitial nephritis may be present. Periglomerular granulomatous inflammation is a non-specific finding, but isolated interstitial granulomas not associated with rupture of Bowman capsule or necrotizing arteritis are thought to be specific for Wegener granulomatosis or Churg-Strauss syndrome in the setting of crescentic GN. Necrotizing arteritis is seen in up to 20% of cases. With the possible exception of interstitial granulomas, the renal pathologic features of Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and renal limited vasculitis are indistinguishable. Most patients with pauci-immune crescentic GN in association with an underlying malignancy demonstrate positive anti-neutrophil cytoplasmic antibody titers, but a few anti-neutrophil cytoplasmic antibody–negative cases have been reported. In rare instances, Wegener granulomatosis alone may present as a renal mass.

The other pathologic entities that can lead to crescentic GN are anti-GBM disease and immune complex–mediated GNs that have been discussed previously (see above). Of these entities, anti-GBM disease is the least common, and there is one putative case in the medical literature in association with RCC. The diagnosis of anti-GBM disease is established by the presence of strong linear IgG staining of the GBM, which will be substantially more intense than albumin.

Systemic vasculitis of extrarenal small and medium-sized arteries has been reported in association with an oncocytopathy and RCC. A variable range of clinical outcomes from no response to complete remission of the vasculitic injury has been observed after resection of the renal neoplasm.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Focal segmental glomerulosclerosis (FSGS) is the most common primary cause of adult nephrotic syndrome. Focal segmental glomerulosclerosis has been identified in up to 9% of tumor nephrectomies and is associated with hypertension, arteriosclerosis and parenchymal scarring, or pyelonephritis. Eajaz et al. describe a patient with RCC who developed progressive renal dysfunction 1 year after unilateral nephrectomy due to probable primary FSGS, which was initially overlooked and identified retrospectively.

Idiopathic or primary FSGS is caused by injury of the glomerular podocytes and characteristically manifests with nephrotic syndrome. Secondary FSGS arises because of structural or functional renal alterations, which can be categorized into 3 broad categories: (1) a response to reduction of functional nephron mass due to primary glomerular or tubulointerstitial disease of vascular, infectious, immunologic, hereditary, or congenital origin; (2) secondary to glomerulonephritis, with the consequence of postinflammatory segmental glomerular scarring; and (3) secondary to hereditary basement membrane defects, such as Alport syndrome.

Focal segmental glomerulosclerosis is characterized by segmental consolidation with capillary occlusion or collapse of the glomerular tuft (Figure 9). Consolidated segments have foam cells, mononuclear inflammation, and accumulation of extracellular matrix. The affected segments also have prominence or proliferation of visceral epithelium, often with cytoplasmic proteinaceous droplets. A working morphologic classification has recently subdivided FSGS into the collapsing, tip lesion, cellular, perihilar, and not otherwise specified variants. The collapsing variant should be distinguished from ischemic collapse, which typically has global shrinkage of the glomerular tufts, with wrinkling of the GBM, periglomerular fibrosis, and absence of podocyte hypertrophy or hyperplasia. Immunofluorescence microscopy may reveal nonspecific trapping of larger molecules like IgM, C3, and sometimes C1q in the sclerosed or hyalinized glomerular regions. Electron microscopy reveals variable effacement and occasional microvillous transformation of podocyte foot processes with or without podocyte detachment from the GBM. No pathologic features can definitively distinguish between primary and secondary forms of FSGS.

The pathogenic mechanisms of FSGS remain to be elucidated, but mutations in various podocyte proteins, including those of the slit diaphragm, can cause FSGS in animal models and humans. Although FSGS is frequently found in association with RCC, this is likely secondary to the advanced parenchymal injury that is frequently present in tumor nephrectomy specimens or the coincidental occurrence of 2 common diseases. Although it is possible that FSGS could be a paraneoplastic manifestation of the underlying renal neoplasm, the removal of the neoplasm has not been demonstrated to improve the extent of proteinuria or delay the progression of renal dysfunction.

MINIMAL-CHANGE DISEASE (PODOCYTOPATHY)

Minimal-change disease is characterized clinically by the presence of nephrotic syndrome or nephrotic-range proteinuria (>3 g per day). This podocyte injury, or podocytopathy, has been reported in association with a wide spectrum of neoplasms, including oncocytopathy and RCC. The diagnosis is established by the presence of diffuse effacement of the podocyte foot processes as visualized by EM. Unless the clinical history of proteinuria is present, our algorithm for evaluating the nonneoplastic renal parenchyma might not detect minimal-change disease because we do not recommend that all specimens undergo evaluation by EM, which is necessary to establish this diagnosis. Minimal-change disease would be an important diagnostic consideration in the RCC patient with persistent proteinuria after nephrectomy. If the podocytopathy is related to the underlying RCC, then surgical resection should be the appropriate therapy.

ACUTE INTERSTITIAL NEPHRITIS

Invariably, the glomerular compartment will get much attention during the evaluation of the nonneoplastic portion of kidney. However, the tubulointerstitial compartment may contain important pathologic findings. Variable degrees of interstitial fibrosis and tubular atrophy will be present in nearly all tumor nephrectomy specimens, which are often accompanied by a mixture of mononuclear inflammatory

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cells. When the inflammatory infiltrate is limited primarily to areas of scarring (interstitial fibrosis and tubular atrophy), then the inflammation is considered to be nonspecific. Atrophic tubules are characterized by thickened, wrinkled, duplicated, or frayed tubular basement membranes. The presence of an interstitial inflammatory infiltrate between well-preserved or nonatrophic tubules should raise the diagnostic consideration of acute interstitial nephritis. The findings of aggregates of eosinophils, interstitial edema, or tubulitis (lymphocytes present between the tubular basement membranes and epithelial cells) involving well-preserved tubules are helpful in supporting this diagnosis. Acute interstitial nephritis has been found to involve nearly 4% of tumor nephrectomy specimens. Acute interstitial nephritis is often due to an allergic drug reaction, and the common culprits include antibiotics, diuretics, and nonsteroidal anti-inflammatory drugs.

During the examination of the tubulointerstitial compartment, the presence of a neoplastic hematopoietic process or lymphoproliferative disorder may be encountered. This entity is technically a neoplastic disease, which extends beyond the scope of this review. However, as the focus of this article is to avoid missing any important pathologic diagnoses that may be present in addition to the neoplasm in question, it is worth noting that RCC patients have an increased risk for developing a second primary malignancy, which includes carcinomas of the prostate, breast, colon, bladder, and non-Hodgkin lymphoma. These secondary malignancies may precede, occur synchronously, or occur after the identification of RCC. Although a primary non-Hodgkin lymphoma of the kidney is rare, infiltration of the kidney by either lymphoma or leukemia is common and has been observed in up to 60% of patients at autopsy. Infiltration of the kidney by both non-Hodgkin and, rarely, Hodgkin lymphoma has been reported in RCC patients and has been well reviewed.

XANTHOGRAULOMATOUS PYELONEPHRITIS

Xanthogranulomatous pyelonephritis has been described in association with both urothelial carcinoma and RCC. Histologic features include a prominent mixture of predominantly foamy macrophages, lymphocytes, and plasma cells (Figure 10). The foamy macrophages should be easily distinguished from clear cell carcinoma. The pathogenesis is unclear, but bacterial infection, renal calculi, or other obstructive causes, such as a neoplasm, are usually present. Xanthogranulomatous pyelonephritis is generally a diffuse process, but focal involvement can rarely mimic a renal mass on imaging studies.

MISCELLANEOUS RENAL LESIONS

This review article has focused primarily on the nonneoplastic kidney diseases that are commonly encountered in adult tumor nephrectomy specimens. However, theoretically, any nonneoplastic kidney disease could be present, and a few additional renal diseases that may or may not be related to the neoplastic process will be mentioned briefly in this section. Thin GBM disease has been identified in tumor nephrectomy specimens. The diagnosis is established by measuring the GBMs using EM, and the World Health Organization criteria require that the average thickness should be less than 264 nm. However, this diagnosis must be established on tissue that has been properly fixed for EM studies because processing paraffin-embedded tissues can artifically thin the GBMs. Persistent hematuria after nephrectomy in an RCC patient should raise the consideration of either thin GBM disease or an immune complex–mediated GN, such as IgAN.

We have experienced a single case of fibrillar GN associated with RCC (S. M. Meehan, unpublished data, November 2005). Light microscopic findings included expansion of the mesangial matrix by eosinophilic material and segmental scarring of the glomeruli. The IF microscopy showed granular staining in primarily mesangial areas for IgG and κ and λ light chains. A Congo red stain was negative, and the EM demonstrated randomly arranged and nonbranching fibrils, which had a similar appearance but were thicker (approximately 20 nm) than amyloid fibrils. The renal symptoms did not resolve after RCC resection, and a follow-up kidney biopsy several years later dem-
onstrated worsening of glomerular and tubulointerstitial scarring. The pathogenesis of fibrillary GN remains unknown, but some cases are associated with hepatitis C and, rarely, with an underlying lymphoproliferative disorder; neither cause was found in our case.

Urate nephropathy can be observed in some patients with gout. This entity is characterized by the deposition of needle-shaped urate crystals within tubular lumina of distal tubules and collecting ducts in the renal medulla. We have observed recently urate nephropathy in an RCC patient with a long clinical history of gout (A. Chang, unpublished data, May 2008). Characteristic tophi and abundant deposition of urate crystals (Figure 11) were present within the renal medulla with secondary granulomatous interstitial nephritis. Acute elevations of serum uric acid levels can be observed in patients undergoing chemotherapy for leukemia or lymphoma, which can lead to acute urate nephropathy. Cryoablation of RCC is gaining use as a therapeutic option, and mild elevations of uric acid in urine samples from such patients have been reported, but to our knowledge this treatment modality has not led to documented cases of acute urate nephropathy.

Balcan endemic nephropathy, a familial form of chronic tubulointerstitial nephritis, is associated frequently with urolithal carcinoma of the upper urinary tract. The histologic features are nonspecific and include significant interstitial fibrosis and tubular atrophy, but reported cases have been limited to specific regions of southeastern Europe. Nonetheless, urothelial carcinomas of the upper urinary tract are frequently associated with chronic kidney disease, so the nonneoplastic kidney parenchyma of these specimens in particular should be carefully reviewed.

Algesic nephropathy has been historically associated with urothelial carcinoma and RCC. This entity, which is characterized by long-term usage of analgesic medications and the presence of interstitial inflammation with significant tubulointerstitial scarring, is now uncommon because of the withdrawal of phenacetin as a therapeutic agent.

**ESRD/ACQUIRED CYSTIC DISEASE**

End-stage kidneys are typically small and shrunken and demonstrate diffuse glomerulosclerosis, severe interstitial fibrosis, tubular atrophy, tubular loss, and severe arteriosclerosis. It may be difficult or impossible to determine the original cause of ESRD in these extensively scarred kidneys. After 3 to 4 years of dialysis, most ESRD patients will develop acquired cystic disease. Numerous cysts of variable size typically demonstrate a proximal tubular phenotype and are lined by tubular epithelial cells, which are flattened or have small papillary projections. End-stage renal disease patients with acquired cystic disease have an increased risk for developing RCCs that show a characteristic spectrum of histopathologic features.

**SUMMARY**

Nonneoplastic kidney diseases are commonly encountered in tumor nephrectomy and nephroureterectomy specimens, and their presence may negatively impact the progression of CKD and clinical outcome in these cancer patients. The surgical pathologist may have the first opportunity to identify these diseases, often at a point in time when appropriate intervention may delay the progression of CKD. When diagnosing a benign neoplasm, the status of the nonneoplastic kidney becomes the most important determinant of clinical outcome. Safeguards should be established to ensure that the nonneoplastic kidney parenchyma is not overlooked, which includes adding this important parameter to synoptic reports, obtaining PAS and/or JMS stains prior to microscopic evaluation of the neoplasm, and adopting a systematic approach to the evaluation of the light microscopic tissue sections. The identification of glomerular abnormalities, including mesangial hypercellularity or sclerosis, segmental scarring, crescent formation, glomerulitis, or glomerular basement membrane alterations should lead to additional IF and EM studies. Nearly any nonneoplastic kidney disease can be present in tumor nephrectomy and nephroureterectomy specimens by sheer chance, but DN and arteriopnenephrosclerosis comprise most of these renal lesions. Additional injuries that may be related to the underlying neoplasm or its treatment regimen include TMA, AA amyloidosis, MN, IgAN, MPGN, pauci-immune crescentic GN, FSGS, minimal-change disease, acute interstitial nephritis, and xanthogranulomatous pyelonephritis. Surgical pathologists should be aware of the importance of both correctly classifying the underlying renal or urethelial neoplasm and the concomitant nonneoplastic kidney disease that is likely to be present in these specimens.

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**References**

18. Tsui KH, Shvarts O, Smith RB, Figlin RA, deKernion JB, Belldegrun A.


