Pathology of the Renal Pelvis and Ureter

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The renal pelvis and ureter are tubular structures that facilitate passage of the urine from the kidney to the urinary bladder. Despite their relatively simple architecture, these organs are subject to a wide variety of pathologic processes. In particular, the complex nature of nephro-ureterogenesis accounts for the observed diversity of congenital abnormalities seen at this site, which may lead to urinary reflux, urinary tract infections, and ultimately renal failure. In addition to these congenital abnormalities, chronic exposure to toxins and metabolites within the urine may promote the development of clinically important diseases such as lithiasis, and mucosal metaplasia and neoplasia. Although a number of reported pelviureteral disorders are rarely encountered in clinical practice, many of the more common conditions account for a significant morbidity and mortality in both pediatric and adult populations.

ANATOMY AND HISTOLOGY

The renal pelvis and ureter are fibromuscular tubes lined by mucosa. The ureter is 30 cm long with an average diameter of 5 mm. There are narrowings of the lumen at the ureteropelvic junction where the external and common iliac vessels cross and where the ureter enters the bladder. These are natural sites for obstruction and impaction of stones and are frequently the sites where pathology is observed.1

Urothelium lines the complete length of the renal pelvis and ureter and varies in thickness from two to three cells in the renal pelvis to four to six cells in the ureter. The surface of the urothelium consists of larger cells aligned parallel to the surface (umbrella cells). These have eosinophilic cytoplasm and occasional binucleate forms and mucin-filled vacuoles are seen.2 The surface of the superficial layer is covered by an impervious trilaminar membrane, which is convoluted in the resting nonstretched state.2 Desmosomes are present between cells of the superficial layer and between superficial and intermediate cells. Beneath the superficial layer, cells are aligned perpendicular to the basement membrane, and in thickened epithelium a condensed basal cell layer may be present. Scattered glycogen-filled vacuoles are often present within the deeper layers. It has been demonstrated that the nuclei of cells of the renal pelvic urothelium are larger than those of the bladder. As a consequence of this, caution is required in interpreting dysplasia and carcinoma in situ (CIS) in frozen sections of ureter.

The lamina propria consists of vascular fibrous tissue, which is more condensed toward the deep aspect.1 Scattered elastic fibers are present, which cause folding of the mucosa in the resting state. Beneath the submucosa, bands of smooth muscle form the muscularis propria, which increases in thickness distally (Fig. 4-1). This is arranged into an inner longitudinal layer and an outer circular layer, although this division is not discernible within the renal pelvis and proximal ureter. The passage of urine through the renal pelvis and ureter is facilitated by peristalsis, with an action potential being propagated between myocytes by numerous close contacts or nexuses.1 In the renal pelvis the fibers of the muscularis have a spiral arrangement, which extends into the immediate proximal ureter.1 This spiral arrangement gives rise to a fragmented appearance to the muscularis in histologic sections, and this has been considered, erroneously, to be a diagnostic feature of ureteropelvic junction obstruction. In the renal pelvis the muscularis propria is covered by fat, which blends into the fat of the renal hilum.2 The adventitia of the proximal ureter consists of loose connective tissue containing collagen, fibroblasts, myocytes, and nerve fibers. This is condensed and thickened in the distal ureter to form Waldeyer fascia, which continues as the adventitia of the bladder.

EMBRYOLOGY

The urinary tract develops from intermediate mesoderm, and three separate renal structures form sequentially. Initially the transient pronephros is formed with an associated nephrogenic duct, which opens into the cloaca. With the development of this structure into the mesonephros by week 4, the nephrogenic duct forms the mesonephric duct from which the ureteric bud develops on its dorsomedial surface. The bud elongates caudally and its junction with the mesonephric
During elongation of the ureteric duct, with associated renal ascent, splitting of the ampullary bud may occur. In cases where this splitting occurs early in nephrogenesis or if two separate ampullary buds form along the length of the mesonephric duct, then double renal pelves and ureters will form, giving rise to a duplex collecting system (Fig. 4-2). Typically the vesicoureteral orifice of the upper pole ureter in a duplex system lies medial and caudal to the lower pole orifice, although exceptions to this rule have been reported. When splitting of the ureteric duct is a late event, a bifid ureter forms with two renal pelves, which drain into separate ureters that fuse to terminate in a single vesicoureteral orifice (Fig. 4-3). The site of the junction of bifid ureters depends on timing of the branching of the ureteric duct migrates toward the cloaca to form separate ureteric and Wolffian ducts by week 6. The caudal end of the ureteric duct forms the ampulla, and this fuses with the metanephric mesenchyme. This fusion induces branching of the ampullary bud to form the renal pelvis, calyces, and collecting ducts, and also induces differentiation of metanephric mesenchyme into nephrons and supporting stroma. By week 12 the ureteral muscularis develops, and by week 14 there is recognizable urothelium lining the upper tract.

It has been claimed that the ureter becomes temporarily obliterated during week 6 and recanalization commences in the midportion and extends both proximally and distally. This process of obliteration and recanalization has been questioned, and it has been suggested that this is merely a collapse of the ureteral lumen prior to the onset of urine output by the metanephros. There is a further temporary obstruction of the ureter by the Chawalla membrane that forms as a thin band of epithelial cells across the ureteral orifice during week 6. Persistence of luminal obliteration or of the Chawalla membrane has been implicated as a cause of ureteral valves and ureteral stenosis.

**MALFORMATIONS**

**Agenesis, Duplication, and Ectopia**

Renal agenesis and duplication, and positional abnormalities of the upper tract are the result of growth failure or abnormal branching of the ureteric duct from the mesonephric duct. Total failure of the ureteric duct to develop results in renal agenesis. Bilateral renal agenesis is rare, with a reported incidence of 3.5/10⁵ live births, while unilateral agenesis is more frequently encountered and in one series was detected in 1/1,200 of children on screening. Renal agenesis may also arise when there is failure of the ureteric duct to fuse with the metanephros, and where the ureteric duct may persist to form a blind diverticulum part way along the length of the ureter.

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**Figure 4-1** Distal ureter showing prominence of the inner longitudinal and outer circular layers of the muscularis propria.

**Figure 4-2** Kidney with duplex renal pelves and ureters.

**Figure 4-3** Double renal pelves and ureters fusing superior to the vesicoureteric orifice to form a single ureter.
duct; however, in the majority of cases, this is in the lower third of the ureter and may be sited in the bladder wall. 17

During embryogenesis the developing ureteric duct migrates distally along the mesonephric duct to fuse with the bladder, and the vesicoureteral orifice migrates to its normal trigonal position. If the ureteric duct develops in close proximity to the bladder, then migration of the vesicoureteral orifice extends beyond the trigone in both the caudal and lateral planes. Often the ectopic ureter is inserted more directly into the bladder wall with loss of the valve mechanism and resulting vesicoureteral reflux. 18 In extreme cases the ureteral orifice extends beyond the bladder, and the ureter terminates in the urethra or the genital structures that develop from the mesonephric duct. In females ureteral ectopia is associated with a duplex system in 80% of cases, while in males there is usually a single renal outflow tract. 18 Further, as the ureteric duct takes its origin from the mesonephric duct, upper tract abnormalities are often associated with other malformations of the urogenital system and are found in the prune belly and VATER syndromes and trisomy 21.

Clinical features of congenital abnormalities of the upper tract are variable although there is often reflux and urinary stasis leading to urinary tract infection, lithiasis, and fistula formation. Ureteral duplications are often asymptomatic although cyclic abdominal pain may occasionally be a presenting feature. 17 Ultrasonography is valuable in the demonstration of malformations in utero and in neonates. The role of the pathologist may be to define the anatomic basis of a functional deficiency.

Ureteropelvic Junction Obstruction

Ureteropelvic junction (UPJ) obstruction refers to the significant functional impairment of urinary flow from the renal pelvis to the ureter leading to hydronephrosis (Fig. 4-4). The majority of cases are congenital and occur in the pediatric age group. More rarely the obstruction may be secondary to postoperative or inflammatory strictures, renal stones, and urothelial neoplasms, including fibroepithelial polyps. 19,20 Rarely UPJ obstruction is associated with renal parenchymal neoplasia. There is also a reported association with congenital renal abnormalities in 15% to 20% of patients, 21 with agenesis and cystic renal dysplasia in the contralateral kidney, 22 and with vasculitis. 23 Functional obstruction has also been reported due to extrinsic compression by an aberrant lower pole vessel. This is seen in 16% to 20% of patients with UPJ obstruction with a median age of 67 months at presentation. 24 UPJ obstruction is more likely to be unilateral in adults, while pediatric cases are more frequently bilateral.

Congenital UPJ obstruction affects 13,000 newborns annually in the United States with hospitalization rates of 2.4/100,000 for patients aged ≤18 years. The highest incidence is in children <3 years of age with hospital admission rates of 9.3/100,000 being reported, 19 and in this age group there is a male predominance. 21 Ethnicity appears not to be a significant factor although slightly higher hospitalization rates for UPJ obstruction have been noted for patients of Hispanic origin. 19

Transport of urine from the renal papilla to the bladder is active and dependent on smooth muscle contraction, with some modulation by the autonomic nervous system. 26 In many cases of clinical UPJ obstruction, no identifiable lesion is seen and the impairment is functional. 27 Earlier studies have demonstrated abnormalities at both a cellular and ultrastructural level, and in particular increased interstitial collagen has been implicated, 28 although this is likely to be a secondary effect. Folds in the muscle or overlying mucosa, or the development of kinks or strictures that lead to reorientation of muscle bundles into a predominantly longitudinal pattern, have also been suggested as a pathogenic mechanism for UPJ obstruction. 29,30 Recent reports utilizing S100 protein, CKIT protooncogene protein (CD117), and synaptophysin immunohistochemistry suggest a defect in innervation as the cause of UPJ obstruction. 31 The UPJ is not normally innervated, and in cases of obstruction it is apparent that this segment extends for a longer distance down the proximal ureter. 32 Defective innervation is supported by a finding of increased vasoactive intestinal peptide and decreased levels of synaptophysin and nerve growth factor receptor in UPJ obstruction. 32 Transforming growth factor beta 1 (TGF-β1) has recently been shown to be increased in UPJ obstruction; however, this may be a secondary effect leading to the promotion of extracellular matrix formation and collagen synthesis. 33

Prior to the advent of ultrasound investigations, UPJ obstruction was usually diagnosed during investigations for
Acquired diverticula are probably secondary to chronic infection or ureteral obstruction. Occasionally multiple diverticula may be present, and it has been suggested that these are acquired, being the result of chronic infection. It is recommended that treatment of small acquired diverticula should be directed toward management of the predisposing condition, although larger diverticula may require surgical resection.

Histologically, congenital diverticula contain all three layers of the ureteral wall, while acquired diverticula usually have a thinned mucosal layer.

Paraureteral diverticula originate within the bladder wall, adjacent to the ureteral orifice, and are due to a failure of normal muscle development or a defect in Waldeyer fascia. In some cases, these can expand to involve the ureter with vesicoureteral reflux or outflow obstruction. There is occasionally coexisting renal dysplasia, and an association with pelvicalyceal duplication has been reported. Treatment is surgical and consists of diverticulectomy with or without ureteral reimplantation.

Ureterocele

Ureterocele is the cystic dilatation of the distal ureter that projects into the bladder (Fig. 4-7). This most commonly occurs in Caucasian females, and there is an annual hospitalization rate of 1/10° in the pediatric age group, with 92% of hospital admissions being children under the age of 2 years. The pathogenesis is uncertain and persistence of Chawalla membrane has been suggested, as has abnormality of the ureteral muscularis. It has been estimated that there is an association with a duplex system in 95% of cases in females and 44% of cases in males. Ureterocele associated with duplex ureter usually occurs in the upper pole ureter and is situated more inferiorly than ureterocele that arises from a single ureter. Previously ureteroceles arising in association with duplex ureters have been designated ectopic ureterocele; however, this term is now limited to those with abnormal development of the ureter as opposed to association with a duplex system.
Megaureter is dilation of the ureter. This is considered to be primary if it is the result of a defect of intrinsic smooth muscle. It is most commonly seen in the pediatric age group and is characterized by a ureteral diameter of >7 mm. Megaureter is not a specific diagnosis and may be associated with reflux or outflow obstruction, although a significant proportion is nonrefluxing and nonobstructed. These three categories of megaureter are further subdivided into primary and secondary groups (Table 4-1). The pathogenesis of megaureter is dependent on the type; however, there is an association with abnormalities of the urinary tract, particularly cystic renal dysplasia.

**Refluxing Megaureter**

Refluxing megaureter is characterized by retrograde flow from the bladder into the ureter. This may be unilateral or bilateral and is more common in females. Primary refluxing megaureter results from abnormalities of the vesicoureteral junction, associated with loss of the valve function of the intramural ureteral segment. The histologic features are

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**Table 4-1 CLASSIFICATION OF MEGAURETER**

<table>
<thead>
<tr>
<th>Megaureter</th>
<th>Primary</th>
<th>Secondary</th>
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<tbody>
<tr>
<td>Refluxing megaureter</td>
<td>- Primary refluxing megaureter</td>
<td>- Urethral obstruction</td>
</tr>
<tr>
<td>Obstructed megaureter</td>
<td>- Urethral obstruction</td>
<td>- Neurogenic bladder</td>
</tr>
<tr>
<td></td>
<td>- Intrinsic obstruction (adynamic segment,</td>
<td>- Urethral obstruction</td>
</tr>
<tr>
<td></td>
<td>ureteral stenosis)</td>
<td>- Neurogenic bladder</td>
</tr>
<tr>
<td>Non-refluxing, non-obstructed</td>
<td>- Non refluxing, non obstructed megaureter</td>
<td>- Extrinsic obstruction</td>
</tr>
<tr>
<td>megaureter</td>
<td></td>
<td>- Polyuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infection</td>
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</tbody>
</table>

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ureteroceles that extend beyond the bladder into the bladder neck or urethra. If a ureterocele burrows between the bladder mucosa and muscularis to lie intramurally, the term cecoureterocele is applied.

Ureterocele is associated with dilatation of the proximal ureter and often results in reflux and hydronephrosis. Larger ureteroceles may also obstruct the contralateral ureter or the normal ipsilateral ureter in a duplex system. Obstruction of renal outflow from ureterocele may lead to cystic renal dysplasia or renal scarring, and in 10% of cases hypertension develops.

The histologic features of ureterocele relate to chronicity. The surface mucosa of ureterocele originates from the bladder, while the cyst lumen is lined by ureteral mucosa (Fig. 4-8). The muscularis may show hypertrophy or be attenuated and atrophic, with interstitial edema and variable interstitial fibrosis.

Treatment of ureterocele consists of early prophylactic antibiotic therapy, to minimize the effect of urinary tract infection. Endoscopic puncture may be undertaken as an emergency procedure, followed by surgical excision of the ureterocele and ureteral reconstruction.

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**Figure 4-7** Cystogram showing a ureterocele with typical cobra-head appearance.

**Figure 4-8** Ureterocele. There is hyperplasia of the urothelium with edema, telangiectasia, and chronic inflammation of the grossly thickened lamina propria.
nonspecific with mural thickening, loss of smooth muscle, and an increase in interstitial connective tissue. Widespread collagen deposition is seen, and quantitative studies have shown a predominance of type III (juvenile) collagen. Treatment is dependent on the severity of the reflux and degree of abnormality of the intravesical ureter. In severe cases early reimplantation is required, and in mild cases reflux may cease as the child grows. Secondary refluxing megaureter may be associated with urethral obstruction, neurogenic bladder, prune belly syndrome, and megacystis.

Obstructed Megaureter

Primary obstructed megaureter results from the presence of an aperistaltic ureteral segment situated immediately proximal to the vesicoureteral junction (Fig. 4-9). Ureteral obstruction in these cases is functional as no stricture is seen, and abnormalities of neuromuscular transmission, resulting in an adynamic segment, have been implicated. Histologic findings are nonspecific, and there is often muscle hypoplasia with disorganization of myofibrils. Increased amounts of collagen are present, and in particular, an increase in collagen types I and III has been noted. Hyperplasia of the ureteral muscularis, associated with ectopic insertion, as well as total loss of the muscularis, have been described. Obstructed megaureter is treated by excision of the lower stenotic segment and ureteral reimplantation.

Obstructed megaureter may occur secondary to urethral obstruction (Fig. 4-10), including urethral valves, neurogenic bladder, and external obstruction such as retroperitoneal fibrosis and neoplasia.

Nonobstructed, Nonrefluxing Megaureter

In the majority of cases of perinatal megaureter, there is no evidence of either ureteral obstruction or reflux. The pathogenesis of nonobstructed, nonrefluxing megaureter is unknown although abnormal ureteral compliance or persistence of fetal ureteral architecture, with transient obstruction, have been proposed. This is confined to the distal ureter immediately proximal to the vesicoureteric junction with ureteral dilatation proximal to this, and the dilated segment of the ureter is often fusiform and lacks the tortuosity associated with other forms of megaureter (Fig. 4-11). There is overlap with the histology of obstructed megaureter with interstitial fibrosis, fibrosis of the periureteral sheath, and hypoplasia of the inner (longitudinal) muscle layer being reported.

Management of nonobstructed, nonrefluxing megaureter is usually expectant in the absence of urinary tract infection or loss of renal function. In severe cases, with declining renal function, ureteral reimplantation is undertaken. Secondary causes of nonobstructed, nonrefluxing megaureter may result from conditions leading to polyuria and from bacterial toxins associated with urinary tract infection.
There is also an association with ipsilateral and contralateral cystic renal dysplasia, solitary kidney, and blind ending of the contralateral ureter.

Secondary ureteral stricture is a recognized complication of ureteral endoscopy and pelvic surgery, with an incidence ranging from 0.5% to 3%. Other secondary causes of ureteral stricture are trauma, ureteral infections, including tuberculosis and inflammation in adjacent organs, radiation, ureteral lithiasis; vasculitis and ischemia, amyloidosis, and endometriosis.

Primary tumors of the ureter, especially urothelial carcinoma, usually present with ureteral stricture, and hydronephrosis and stricture may also be seen in association with extraureteral tumors that involve the ureter by direct infiltration or metastatic spread (Fig. 4-12).

Ureteral Valves

Ureteral valves are a rare cause of ureteral outflow obstruction with <60 cases being reported. The majority of cases occur in males in the pediatric age group, with hydronephrosis being the most frequently associated finding. In many cases there is also an association with abnormalities of the kidney and ureters.

The pathogenesis of ureteral valves is debated; however, it has been suggested that they represent a persistent Chawalla membrane or an exuberant form of the ureteral folds seen in normal fetal development.
Specific criteria for the diagnosis of ureteral valves have been proposed; (i) The leaflets should be covered by mucosa and contain smooth muscle, (ii) There should be ureteral obstruction proximal to the fold but not distal to it, and (iii) There should be no other evidence of either functional or mechanical obstruction. The requirement for the identification of smooth muscle in the leaflet is debated, while others require smooth muscle in the leaflet base. Valves may occur throughout the length of the ureter, with 50% reported from the proximal ureter, 17% the mid ureter, and 33% the distal ureter. Histologically, ureteral valves may form leaflets or an annular ring of mucosal-covered connective tissue.

Management of valve leaflets is surgical with most treated by ureteroureterostomy, ureteropyelostomy, or longitudinal ureterotomy.

Ureteral folds are rarely detected on excretory urography, and these occasionally have a corkscrew appearance. These folds consist of lamina propria and smooth muscle and probably represent persistent fetal ureteral tortuosity. Most cases of ureteral folds are not associated with outflow obstruction, although rarely hydronephrosis may be a presenting feature.

INFLAMMATION AND INFECTION

Renal Pelvis and Ureteral Infection

Infection of the upper urinary tract is usually secondary to lower tract infection and may be associated with urinary tract obstruction, voiding dysfunction, and urinary tract abnormalities (ureteral duplication, megaureter, and UPJ obstruction). Other significant contributing factors include catheterization, instrumentalization, and urinary tract lithiasis, while ureteral infection may occur secondary to pyelonephritis.

The most common pathogenic bacterial organism in the urinary tract is Escherichia coli although Proteus, Klebsiella, Enterococcus, Pseudomonas, and Serratia are frequently encountered. Struvite lithiasis is often associated with Proteus and less commonly M organella infection.

Mycobacterium infection of the ureter (Fig. 4-13A and B) is usually secondary to renal infection and may result in the development of stricture leading to hydronephrosis. Mycobacterium tuberculosis is most frequently involved, although M. avium, M. kansasii, and M. bovis infections are also well described.

Upper tract fungal infections are usually associated with systemic disease or localized renal infection in an immunocompromised patient. A wide variety of fungi have been reported as renal pelvis and ureteral pathogens with Candida being the most commonly seen. This may form a fungal bezoar within the renal pelvis and, as is reported for Aspergillus and Coccidioides, may result in ureteral stricture formation. There is a single case report of extragenital granuloma inguinale presenting as a soft tissue neoplasm involving the ureter.

Malacoplakia

While more commonly occurring in the urinary bladder, renal parenchyma, and genital tract, occasional cases of malacoplakia of the renal pelvis and ureter (Fig. 4-13C) have been reported. There is a female predominance with ages of patients ranging from 24 to 78 years (mean 66 years). In the majority of cases, there were no reported preexisting conditions although an association with concurrent acute inflammation and immunosuppression has been noted and there is a single case report of malacoplakia in a transplant ureter.

Malacoplakia of the renal pelvis and/or ureter usually presents as an exophytic tumor-like lesion on imaging and may be mistaken for urothelial carcinoma. Urinary cytology has also been shown to be diagnostic in rare instances. Disease may be bilateral or unilateral and is often associated with urinary obstruction and hydronephrosis. Malacoplakia has also been reported as a cause of secondary UPJ obstruction.

On occasion inflammation may be limited to the renal pelvis or ureter; however, there is usually concurrent malacoplakia in the urinary bladder or renal parenchyma, and it has been suggested that involvement of the urinary outflow tract is a secondary feature.

Grossly the lesion may be solitary or multifocal and is soft friable and exophytic ranging from white to pale yellow in color.

Histology shows typical features of malacoplakia with early lesions resembling xanthogranulomatous inflammation without Michaelis-Gutmann bodies, while later lesions may be associated with interstitial fibrosis. On ultrastructural examination both histiocytes and urothelial cells contain cytoplasmic multilamellar bodies.

Few reports have identified organisms within foci of malacoplakia although E. coli has been isolated, and treatment usually involves either localized or radical resection with adjuvant antibiotic therapy. Occasionally antibiotic treatment alone, or in combination of ureteral stenting, is successful.

Renal Pelvis and Ureter Lithiasis

Renal lithiasis is a common problem, especially in Western countries, and is increasing in frequency. Within the United States, it is estimated that 13% of males and 7% of females will be diagnosed with a renal stone and that the likelihood of recurrence is up to 50% on a 5-year follow-up. The advent of nonsurgical treatments has led to a decline in hospitalization for renal lithiasis although in 2000, 62/100,000 population were treated as inpatients for upper tract stones in the United States, with the rates being highest for the 55- to 64-year age group.

Stone composition is variable (Table 4-2) and in the majority of instances stones form as the result of metabolic disorders, dietary factors, and/or urinary tract abnormalities, although medications such as adenosine, ephedrine, indinavir, and triamterene have been implicated. There is a strong...
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Figure 4-13  A: Ureteral tuberculosis with transmural thickening. B: Granulomas in ureteral tuberculosis. C: Malacoplakia involving the ureter. (Illustration courtesy of Dr. D) Grignon.)

Table 4-2  FREQUENCY OF TYPE OF UPPER TRACT STONE

<table>
<thead>
<tr>
<th>Stone Type</th>
<th>Frequency</th>
</tr>
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<tr>
<td>Calcium oxalate and phosphate</td>
<td>34%</td>
</tr>
<tr>
<td>Calcium oxalate</td>
<td>33%</td>
</tr>
<tr>
<td>Magnesium ammonium phosphate (struvite)</td>
<td>15%</td>
</tr>
<tr>
<td>Uric acid</td>
<td>8%</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>6%</td>
</tr>
<tr>
<td>Cystine</td>
<td>3%</td>
</tr>
<tr>
<td>Others</td>
<td>1%</td>
</tr>
</tbody>
</table>


genetic predisposition to some forms of nephrolithiasis, and genes associated with cystinuria, hyperoxaluria, and X-linked nephrolithiasis have been identified.103 In many cases multiple genetic loci are involved and this reflects the many and diverse causes of hypercalciuria. A separate pathogenesis is described for struvite stones, which form as a result of chronic bacterial infection of the urinary tract, with the presence of urea-splitting bacteria being necessary for the generation of inorganic carbonate and phosphate.104

The natural history of stones within the renal pelvis and ureter is dependent on stone type and the metabolic environment. In general terms calyceal stones are asymptomatic
when small, but if untreated, almost 50% will become symptomatic in 5 years. Larger stones within the renal pelvis may present with urinary tract infection, pain, hematuria, dysuria, and obstruction, especially at the UPJ (Fig. 4-14).

Ureteral stones (Fig. 4-15) are often symptomatic, and impaction, with urinary outflow obstruction, may be a presenting feature. Stones >5 mm in diameter usually require intervention as they are unlikely to pass spontaneously, and complications include localized mucosal ulceration and edema, leading to scarring and stricture formation, or ureteral perforation.

The pressure effect of renal stones on the mucosa of the renal pelvis is compounded by recurrent acute or chronic inflammation. This results in mucosal ulceration, reactive hyperplasia of adjacent urothelium, granulation tissue formation, and fibrosis. Chronic inflammation predisposes to reactive epithelial changes with a predominance of squamous metaplasia. Other benign mucosal changes reported from the renal pelvis in association with renal lithiasis are pyelitis follicularis, pyelitis cystica, polypoid pyelitis, xanthogranulomatous pyelitis, encrusted pyelitis, and fibroepithelial polyposis. Similar changes are seen in the ureter with chronic inflammation being associated with squamous metaplasia, ureteritis follicularis, ureteritis cystica, and polypoid ureteritis.

Renal lithiasis is a recognized risk factor for renal pelvic and ureteral malignancy. The risk of developing malignancy is enhanced by recurrent urinary tract infections and is most commonly associated with struvite staghorn calculi. In some series the risk of malignancy increased with chronicity, while in others the risk remained stable over a 10-year follow-up. Urothelial carcinoma (UC) is the tumor most frequently associated with lithiasis, although squamous cell carcinoma (SCC) occurs in 20% of cases and has been found in 2% of patients with recurrent staghorn calculi. In addition to these tumors, verrucous carcinoma, sarcomatoid SCC, small cell (neuroendocrine) carcinoma, and adenocarcinoma have been reported.

Vasculitis

Although the kidney is the most common organ to be involved in many of the forms of systemic vasculitis, reports of vasculitis of the renal pelvis and ureter are rare and are usually confined to single cases. Vasculitis of the urinary outflow tract often occurs as part of multisystem disease and presents as UPJ obstruction or ureteral stenosis, which may be unilateral or bilateral, with secondary hydronephrosis.

Renal pelvic or ureteral vasculitis has been reported as part of the polyarteritis group of systemic vasculitis (classic polyarteritis nodosa, polyarteritis nodosa associated with hepatitis B, and acute febrile mucocutaneous lymph node syndrome); as well as with Henoch-Schönlein hypersensitivity angiitis. In these cases ureteral stenosis was associated with typical clinical and pathologic systemic features. Renal pelvic and ureteral vasculitis has also been noted in Churg-Strauss syndrome and Wegener granulomatosis in patients with established pulmonary disease. Limited Wegener granulomatosis, involving the urogenital tract, has also been associated with ureteral vasculitis.

Ureteral angiitis as part of the systemic manifestation of rheumatic connective tissue disease occurs rarely and has
been noted in cases of systemic sclerosis, systemic lupus erythematosus, and dermatomyositis.

Renal Pelvis and Ureter Injury

Trauma

Renal injury occurs in up to 3% of major trauma; however, direct involvement of the renal pelvis is rare. In cases of blunt or penetrating trauma to either the UPJ or renal pelvis, there is usually hematurnia and urinary extravasation may occur. Rarely a urinoma may form and this can become secondarily infected. Ureteral trauma is most frequently iatrogenic, with gynecologic procedures predominating and in those cases requiring reconstruction, outcome is predicted by the length of ureteral injury and a history of previous radiotherapy. In cases of noniatrogenic ureteral injury in the United States, 81% result from gunshot wounds, while 10% are related to blunt trauma and 9% to stab wounds.

Radiation

Ureteral stenosis has been reported in 0.3% of patients with a mean follow-up of 5.7 years following curative radiotherapy for gynecologic carcinomas. In the acute phase following radiotherapy, ureteral dilation occurs in two-thirds of cases, and this usually resolves over 6 months. In experimental animal models asymptomatic fibrotic ureteral stenosis was observed in dogs following doses of 20 Gy, and this has been associated with increased levels of TGF-β.

High-dose radiation is associated with capillary thrombosis, and in early lesions epithelial atypia and mucosal ulceration are seen. Chronic effects consist of cytoplasmic vacuolation of epithelial cells, loss of pleating with associated telangiectasia of ureteral mucosa, submucosal chronic active inflammation and fibrosis (Fig. 4-16), ureteritis cystica, and squamous metaplasia. In experimental animal models these changes have been shown to increase in severity for the first 12 months following radiotherapy. In these studies the resulting stenosis was found to be functional as secondary hydronephrosis developed in the presence of a patent ureter. Ureteral UC has been reported as a secondary effect of radiation, and renal pelvis SCC has also been noted.

Renal Pelvis Hemorrhage

Hemorrhage into the renal pelvis may be associated with subepithelial hematoma (Antopol-Goldman lesion). Often misdiagnosed as renal pelvic neoplasia, 25 cases of subepithelial hematoma have been reported. There is a female predominance with the ages of patients ranging from 24 to 84 years. In several cases the cause of the hematoma could not be determined, while in others it was shown to be secondary to trauma, hypertension, analgesic abuse, or coagulopathy. In five cases subepithelial hematomas were associated with congenital renal abnormalities. Histologic findings are nonspecific and consist of subepithelial hemorrhage, which may be associated with peripelvic hemorrhage, renal cortical infarction, or hydronephrosis. The majority of cases have been treated by nephrectomy or partial nephrectomy; however, once the diagnosis is established, conservative therapy is advocated.

Renal Pelvis and Ureter Injury

Trauma

Renal injury occurs in up to 3% of major trauma; however, direct involvement of the renal pelvis is rare. In cases of blunt or penetrating trauma to either the UPJ or renal pelvis, there is usually hematurnia and urinary extravasation may occur. Rarely a urinoma may form and this can become secondarily infected. Ureteral trauma is most frequently iatrogenic, with gynecologic procedures predominating and in those cases requiring reconstruction, outcome is predicted by the length of ureteral injury and a history of previous radiotherapy. In cases of noniatrogenic ureteral injury in the United States, 81% result from gunshot wounds, while 10% are related to blunt trauma and 9% to stab wounds.

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Hemorrhage into the renal pelvis, in the absence of subepithelial hematoma or neoplasia, has been associated with coumadin anticoagulant therapy and has been recognized as a complication of retrograde endopyelotomy.

Retroperitoneal Fibrosis (Sclerosing Retroperitoneal Fibrosis)

Retroperitoneal fibrosis is typically a diffuse fibrous process that involves the aorta, vena cava, and structures of the retroperitoneum. It may be primary or idiopathic or in approximately 25% of cases is secondary to autoimmune diseases, malignancy, trauma and surgery, chronic infection, drugs (methysergide, pergolide, ergotamine, methyldopa, hydralazine, and beta-blockers), and radiation. The majority of cases have been treated by nephrectomy or partial nephrectomy; however, once the diagnosis is established, conservative therapy is advocated.

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The pathogenesis of retroperitoneal fibrosis is uncertain, and the association of secondary forms of the disease with hyperimmune states suggests an autoimmune etiology. There is also a reported association with asbestosis, autoimmune thyroid disease including Riedel thyroiditis, Wegener granulomatosis, mediastinal fibrosis, polyarteritis nodosa, systemic lupus erythematosus, sclerosing cholangitis and primary biliary cirrhosis, UC, and sclerosing lymphoma.

Clinical features are nonspecific and relate to the structure encased in fibrous tissue. Often there is ureteral involvement, and in neglected cases renal failure is a common complication. Laboratory results are similarly nonspecific.
with elevated C-reactive protein and erythrocyte sedimentation rate, as well as positive antinuclear antibodies being the most frequent findings.

Macroscopically, retroperitoneal fibrosis consists of white fibrous plaques that encase retroperitoneal structures. The fibrosis is usually diffuse; however, in occasional cases the fibrosis is confined to single organs, and localized ureteral (Fig. 4-17A) and perirenal retroperitoneal fibrosis has been reported. On microscopic examination (Fig. 4-17B) the lesions consist of sheets of fibroblasts showing variable cellularity. There is frequently an associated inflammatory infiltrate consisting predominantly of lymphocytes and plasma cells. In older lesions the inflammatory cell infiltrate is less prominent, and there is hyalinization, occasionally with dystrophic calcification. Vascular changes resembling vasculitis, with intramural inflammatory cells and fibrinoid necrosis, are often present.

In the majority of cases, there is both a symptomatic and clinical response to steroids with a resulting decrease in the volume of fibrous tissue. Stenting of ureters is frequently necessary, and in cases refractory to steroids, surgical intervention, consisting of ureteral replacement and autotransplantation of the kidney may be required. Often the disease relapses and long-term follow-up is necessary. In cases of secondary retroperitoneal fibrosis, treatment of the primary disease process may lead to a reduction in the volume of fibrous tissue.

Reactive Atypia Due to Instrumentation, Stents, and Strictures

Biopsies from patients with stents or strictures and after instrumentation can have atypical changes mimicking urothelial CIS. In contrast to urothelial CIS, reactive atypia displays cellular and nuclear enlargement with prominent nucleoli and mitotic activity in the absence of significant pleomorphism and chromatin abnormalities. Immunohistochemistry (CK 20, P53, and CD 44) may be helpful however, correlation with morphology is critical due to overlap in immunoprofile in reactive versus neoplastic conditions.
Endometriosis and Müllerianosis

Endometriosis, the benign proliferation of ectopic endometrial mucosa, involves the urinary tract in 2% of reported cases. In most of these instances, endometriosis is confined to the urinary bladder; however, in 16% of cases one or both ureters are also involved. In most cases of urinary tract endometriosis, symptoms of dysuria, frequency, recurrent urinary tract infection, and/or renal angle pain are reported, although endometriosis confined to the ureter is asymptomatic in 60% of patients.

In endometriosis diffusely spread within the pelvis and in the urinary tract, lesions are more commonly found on the left side, and it has been speculated that this is a reflection of the direction of flow of peritoneal fluid that carries regurgitated endometrial tissue to ectopic sites.

In 65% of cases involving the ureters, endometriosis is superficial within the overlying peritoneal tissues, and in a further 30% of cases, the endometriotic deposits lie adjacent to the ureter. Intramural endometriosis is present in only 5% of lesions, and these are usually associated with ureteral stenosis.

The histologic features of ureteral endometriosis are similar to those seen in other organs. Recognizable endometrial epithelium and stroma may be present, or there may be recent hemorrhage and/or aggregates of hemosiderin and hemosiderin-laden macrophages (Fig. 4-18). In the latter instance CD10 immunohistochemistry is often useful for detecting small foci of residual endometrial stroma. Rarely, Müllerianosis with endocervicosis or endosalpingiosis can be seen as ureteric lesions. In some cases there is associated endometriosis.

Rarely endometrioid adenocarcinoma may arise in ureteral endometriosis, and in one reported case there was no evidence of residual endometriosis in the genital tract or elsewhere in the urinary tract.

Management of endometriosis of the ureter is dependent on the site of the lesion. Peritoneal deposits are amenable to laparoscopic excision, while intramural endometriosis may require ureteral resection and anastomosis.

Amyloidosis

Primary localized amyloidosis is rarely seen in the urinary tract with <50 reported cases involving the renal pelvis and ureter. There is a male predominance, and patients are usually >50 years of age, with pyrexia, hematuria, and flank pain being common presenting features. On imaging, ureteral stricture and hydronephrosis are frequent findings. This may be unilateral or bilateral and in most cases mimics invasive UC. Although urinary cytology may provide evidence of the correct diagnosis, most cases are diagnosed following surgery.

Histologically, amyloid deposits are interstitial and most commonly involve the lamina propria and muscularis. The amyloid is usually of the AL type, as demonstrated by congophilia with resistance to permanganate treatment, and on immunohistochemistry consists of lambda light chains. Rarely osseous metaplasia may occur. Management usually involves surgical resection of the involved segment.

Hyperplasia and Metaplasia

Pyeloureteritis Cystica and Glandularis

Pyeloureteritis cystica is a cystic dilation of mucosal urothelial nests (Brunn nests) and is the renal pelvic and ureteral equivalent of cystitis cystica. This may be a variant of normal histology as it is present in up to 10% of normal ureters at autopsy. Pyeloureteritis cystica is usually asymptomatic and is more commonly found in female patients and in the elderly. There is an association with chronic or recurrent infection (including schistosomiasis), lithiasis, and chemical irritants such as formalin instilled for treatment of cyclophosphamide-induced cystitis. Although occasionally associated with UC and adenocarcinoma, long-term follow-up suggests that pyeloureteritis cystica has no malignant potential and represents a reactive response to chronic mucosal irritation.

In both the renal pelvis and ureter, cystic lesions are either confined to the mucosa or form polyps covered by urothelium with a loose connective tissue stroma and may be visible on radiologic imaging. Intramural cysts are lined by urothelium, which, in the case of larger cysts, may become attenuated, and there is usually an associated chronic inflammatory cell infiltrate (Fig. 4-19). Transition of urothelium to mucus-secreting and columnar epithelium similar to that of the colon is known as pyeloureteritis glandularis, and this has been suggested as a precursor to adenocarcinoma.

Various treatments have been recommended, and in the bladder resolution of cystitis cystica has been noted following installation of 2% silver nitrate and with long-term antibiotic treatment.
Unusual forms of urothelial metaplasia have been reported. Müllerian metaplasia has been noted in the ureter of an otherwise well 39-year-old female. This was characterized by metaplasia of surface epithelium, and additionally Müllerian epithelium–lined cysts were present within the lamina propria. Osseous metaplasia within the ureter is rare and in animal models has developed in response to ischemia, necrosis, fibrosis, and trauma. In single cases osseous metaplasia has been reported in association with amyloidosis and trauma and has also been observed in the ureter of a donor kidney, post-transplantation. Foci of osseous metaplasia may occasionally act as a nidus for the formation of stones within the renal pelvis and ureter.

Nephrogenic Adenoma

Nephrogenic adenomas are benign lesions of the urothelium and lamina propria. The majority of cases are confined to the bladder; however, in various series 11% to 31% were present in the renal pelvis and ureter, respectively. There is a male predominance and the age of patients ranges from 9 to 75 years, which is a similar age distribution for nephrogenic adenoma of the bladder. The pathogenesis is uncertain although the frequent association with coexisting chronic inflammation and stones supports the suggestion that nephrogenic adenoma is a form of urothelial metaplasia. It has also been shown that some of the lesions result from implanted renal tubular cells. Glandular metaplasia usually occurs within foci of pyeloureteritis cystica, with formation of colonic-type epithelium, which may contain Paneth cells and intraluminal mucin. Goblet cell metaplasia and diffuse glandular metaplasia are infrequently seen (Fig. 4-20) and most commonly develop in association with lithiasis and chronic infection. Glandular metaplasia may present as a polypoid or sessile mass, and on occasion colonic-type glands may be implanted within the lamina propria mimicking invasive carcinoma. In such cases the benign nature of the epithelium may be determined by a uniform lack of nuclear atypia. There is, however, an association between glandular metaplasia and adenocarcinoma, and this has been reported for both pyeloureteritis glandularis and diffuse glandular metaplasia.

Pyeloureteral Urothelial Hyperplasia and Metaplasia

Irritation of the renal pelvis and ureter may result in epithelial hyperplasia or metaplasia. Hyperplasia of the surface epithelium leads to a thickened flat overgrowth of urothelium. This is seen as a reactive phenomenon but is rarely present in bladders with coexisting low-grade urothelial neoplasms. In cases where irritation is chronic, squamous metaplasia of the urothelium (leukoplakia) may develop. This is most commonly associated with mechanical stimuli such as lithiasis, although an association with radiation, xanthogranulomatous pyelonephritis, and recurrent infection, including schistosomiasis, is well recognized. Squamous metaplasia is more frequently seen in females, and there is a slight predominance of left-sided lesions; however, unlike those seen in the bladder, pyeloureteral lesions are usually focal. There is often hyperkeratosis and in these cases the term cholesteatoma has been applied, and occasionally dystrophic calcification may also develop. The underlying lamina propria usually contains a variable chronic inflammatory cell infiltrate, and foreign body–type giant cells may develop as a response to the implantation of keratin. There is often atypia of metaplastic epithelial cells, and in 8% to 12% of cases there is an associated SCC. Glandular metaplasia usually occurs within foci of pyeloureteritis cystica, with formation of colonic-type epithelium, which may contain Paneth cells and intraluminal mucin. Goblet cell metaplasia and diffuse glandular metaplasia are infrequently seen (Fig. 4-20) and most commonly develop in association with lithiasis and chronic infection. Glandular metaplasia may present as a polypoid or sessile mass, and on occasion colonic-type glands may be implanted within the lamina propria mimicking invasive carcinoma. In such cases the benign nature of the epithelium may be determined by a uniform lack of nuclear atypia. There is, however, an association between glandular metaplasia and adenocarcinoma, and this has been reported for both pyeloureteritis glandularis and diffuse glandular metaplasia.

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Occasionally ureteral nephrogenic adenoma may lead to proximal ureteral dilatation and hydronephrosis, necessitating endoscopic removal. Preexisting conditions associated with ureteral nephrogenic adenoma include neuropathic bladder, tuberculosis, and UC and cytomegalovirus infection in renal transplant patients. The histologic features of ureteral and renal pelvic nephrogenic adenoma are similar to those of lesions found elsewhere in the urinary tract (see Chapter 5).

### Polyps, Cysts, and Other Pseudotumors

#### Fibroepithelial Polyps

Fibroepithelial polyps are benign mucosal lesions which rarely occur in the ureter and renal pelvis. The etiology of most fibroepithelial polyps is obscure, but many are considered to be either of congenital or inflammatory origin and are often associated with calculi.

Polyps usually occur in young to middle-aged adults, but can also occur in children and the elderly, with a higher frequency in males. Patients present with flank pain, hematuria, or evidence of UPJ obstruction. A filling defect is usually seen on intravenous urography.

Polyps occur most commonly in the renal pelvis, proximal ureter, or UPJ. Grossly, one or more fleshy soft polyps may be present, and most are round or bilobed and lobulated (Fig. 4-21). Histologically the polyps are characterized by exophytic projections of fibrous tissue covered by urothelium with varying degrees of inflammation (Fig. 4-22).

#### Cysts

Cysts reported in the upper urinary tract include epidermoid cysts of ureter and parapelvic cysts.

#### Inflammatory Pseudotumor

Inflammatory pseudotumor, also known as pseudosarcomatous myofibroblastic proliferation, inflammatory myofibroblastic tumor, and postoperative spindle cell nodule, occurs rarely in the upper tract. In contrast to visceral and soft tissue lesions, which occur predominantly in children and young adults, inflammatory pseudotumor of the urinary tract occurs in a wide age range, but predominantly in adults. These lesions from elsewhere in the urinary tract have been shown to have anaplastic lymphoma kinase (ALK) gene alterations; however, no case reported from the ureter or renal pelvis has shown immunostaining for ALK rearrangements. Although no recurrences or metastases were reported in a series of cases involving the renal pelvis, one case involving the ureter and renal pelvis was associated with sarcomatoid UC.

Inflammatory pseudotumor is characterized by a proliferation of spindle cells admixed with a chronic inflammatory cell infiltrate, similar to that seen in other locations. Three histologic patterns have been reported with lesions being described as myxoid vascular, compact spindle cell, and hypocellular fibrous. The spindle cells in inflammatory pseudotumor display myofibroblastic characteristics and are positive for vimentin and smooth muscle actin and variably express HHF-35, cytokeratins, desmin, and CD68.

### Neoplasms

The renal pelvis and ureter give rise to a variety of benign and malignant neoplasms of both epithelial and mesenchymal types. These account for about 9% of all urinary tract neoplasms and 10% to 15% of renal tumors. Carcinomas arising in this location are derived from the urothelium and are therefore similar to bladder cancers. Compared to bladder cancers, however, these tumors are less common and may be associated with several familial syndromes. Other differences include the relative inaccessibility of the renal pelvis and ureter to topical therapies and, given the anatomical differences such as thickness of the muscularis, the possibility of early metastatic spread. More than 90% of renal pelvic and ureteral carcinomas are UCs, with adenocarcinoma and SCC being more rarely encountered. Similar to those of the bladder, pelviureteral tumors are more common in males and in older patients.
**Epithelial Tumors: Benign**

**Urothelial Papilloma**

Rare cases of pelviureteral urothelial papillomas have been reported in children and adults. These are usually found incidentally although some may present with hematuria, and radiologically a filling defect is usually seen. These are mostly small lesions measuring a few millimeters in diameter and being treated by fulguration are not usually sent for histopathologic evaluation.

Histologically these delicate papillary lesions have a thin fibrovascular core covered by benign urothelium of normal thickness.

**Inverted Papilloma**

Pelviureteral inverted papillomas are rare and more frequently seen in the ureter than in the renal pelvis. These occur in adults and there is a male predominance. Some inverted papillomas present with gross or microscopic painless hematuria, flank pain, or colic or may be detected as a filling defect seen on intravenous urography.

Inverted papillomas of the renal pelvis and ureter are either sessile or pedunculated polyps, usually measuring <3 cm in maximum dimension and having a similar histology to those seen in the bladder.

Inverted papillomas are benign neoplasms usually treated by local excision. However, the long-term outcome is unknown. Some cases are associated with multicentricity and coexistent malignancy, and for these reasons, long-term follow-up is recommended.

**Villous Adenoma**

Tumors similar in morphology to villous adenoma of the colon occur in the urinary tract, with rare examples reported in the ureter and renal pelvis. These tumors occur in adults with a similar incidence in males and females. There is an association with renal calculi, long-standing chronic inflammation, and intestinal metaplasia, and patients usually present with hematuria or flank pain. A bandunt mucus production and mucus retention causing distension of the renal pelvis (muconephrosis) and proximal ureter may also occur. Histologically these are papillary exophytic tumors with pointed or blunt, finger-like processes lined by pseudostratified columnar epithelium displaying variable atypia (Fig. 4-23). Most adenomas have cytoplasmic mucin and are positive for cytokeratins CK7 and CK20, while some are positive for carcinoembryonic antigen and epithelial membrane antigen (EMA). Patients without coexistent adenocarcinoma have an excellent prognosis with no recurrence being reported after local excision. Given the rarity of reported cases in the upper tract, it is advisable that these patients are followed closely, even after apparent complete excision of the lesion. If the lesion is not entirely submitted for examination, a definite diagnosis of villous adenoma should not be made as there is a risk of missing deeper and occult adenocarcinoma.

**Epithelial Tumors: Malignant**

**Urothelial Carcinoma**

**Epidemiology**

UC of the renal pelvis and ureter accounts for about 5% of all urothelial tumors of the urinary tract. Two-thirds of the upper tract tumors occur in the renal pelvis, while most ureteral cancers occur in the distal ureter. Pelviureteral UC is multifocal in about one-third of patients, but bilaterality is uncommon, seen in only about 3% of patients. These tumors are twice as common in males as in females and twice as common in whites as in African-Americans. The mean age at presentation for UC is 65 years, and tumors are rare in those <40 years of age. The incidence of tumors is 0.6 to 1.1 per 100,000 person-years and varies worldwide, with the highest rates found in Australia, North America, and Europe and lowest rates in South and Central America and Africa. In recent years, there appears to have been an increase in the incidence of UC. Other studies report an increase in situ carcinoma ranging from 7.2% to 23.1% and in invasive ureteral cancers from 0.69 to 0.73 per 100,000 person-years, but no change in the incidence of renal pelvic tumors. This apparent increase has coincided with an increase in ureteroscopic procedures, but may also be associated with increased environmental exposure to carcinogens as well as the effects of an aging population.
The incidence of UC of the upper tract after bladder cancer varies between 2% and 13.4%, with most upper tract tumors found within 3 to 6 years after the diagnosis of the bladder primary. The risk is significantly higher in patients with high-grade tumors, multifocal tumors, urothelial CIS, and urethral involvement, and patients with CIS of the bladder and upper tract involvement show high rates of tumor bilaterality.

**Etiopathogenesis**

**Genetic Susceptibility.** A familial risk has been found in some patients with upper tract UC whose carcinomas have identical karyotypic profiles to those of bladder UC. Rearrangements of chromosome 9 resulting in loss of material from 9p, 9q or of the entire chromosome are the most frequent alterations, seen in 50% to 75% of all patients. Loss of material from chromosome arms 1p, 8p, and 11p, with gains of chromosome 7, 1q, and 8q seem to be early changes occurring in superficial low-grade tumors, whereas loss of material from 17p, formation of isochromosome 5p, and p53 mutations are seen in more aggressive, invasive tumor phenotypes. Mutations of FGFR3, KRT20, UPK2, FXD3, 3 hTERT, and BIRC5 have also been reported. Upper tract UC may also develop as a component of the hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome), which is characterized by germline mutations in a number of DNA mismatch repair (MMR) genes, detectable as microsatellite instability (MSI) or loss of the respective protein by immunostaining. MSI occurs in 20% to 31% of patients with upper tract UC, although a recent population-based study from Sweden found an incidence of only 6% in these tumors. About 90% of cases show loss of MMR proteins hMSH2, hMLH1, or hMSH6, and in 7% to 33% of cases, there is alteration of coding sequence microsatellites (TGFbetaRII, Bax, hMSH3, and hMSH6). These tumors have been shown to have significantly different clinical findings from sporadic upper tract UC, including a high prevalence in females and characteristic histopathologic features such as frequent papillary and inverted growth patterns. In one study, an inverted morphology of at least 20% of the tumor was found in 65.7% of microsatellite-unstable tumors, compared with only 17.5% of microsatellite-stable tumors. Inverted growth in upper tract urothelial cancers may serve as a marker lesion for MSI and may assist in identifying patients who should be tested for HNPCC. Some studies have shown a low tumor stage and grade for these tumors, while a recent study has shown a high-grade potential similar to that in the general population with an almost equal gender ratio. These occur at a younger age and are more likely to be in the ureter (Box 4-1).

**Tobacco Smoking.** Significantly increased relative risks for development of upper tract UC are seen in smokers compared with nonsmokers. The risk of urothelial cancer in smokers is higher in the ureter than in the renal pelvis and is higher in the renal pelvis, when compared to the urinary bladder.

**Occupational Exposure.** There are several occupational exposures linked to renal pelvic cancers. The dry-cleaning, iron, and steel industries are reported as high-risk occupations, and significantly increased risks have also been reported in the petrochemical, chemical, and plastic industries and from exposure to coal and coke, asphalt, and tar.

**Analgesic Abuse.** Chronic abuse of analgesics, and especially that of phenacetin, is an established risk factor for carcinoma of the upper urinary tract. Regular consumption of phenacetin-containing analgesics confers a 10-fold relative risk in women and four- to eightfold relative risks in men for the development of renal pelvic cancer. There also appears to be an increased risk from aspirin use among women. There is a synergistic effect, when there is both analgesic abuse and tobacco smoking, with a reduction in the incidence of renal pelvic cancer resulting from cessation of both risk factors. A history of analgesic abuse is strongly associated with the presence and severity of diffuse renal papillary scarring with thickening of the basement membrane around subepithelial capillaries (capillary sclerosis), and this lesion confers an increased risk of UC. For both phenacetin and aspirin, a dose effect has been observed as moderate consumption doubles the risk of renal pelvic cancer, and heavy consumption increases the risk to 6 to 16 times that for nonconsumers. The histologic grade of the tumors also tends to rise in a dose-dependent fashion. Patients with renal transplants for end-stage analgesic nephropathy also have an increased risk of upper tract UC in the transplanted kidney.

**Balkan Endemic Nephropathy.** Balkan endemic nephropathy (BEN) is a chronic tubulointerstitial nephritis with notable concentric atrophy of the ureter and renal cortex. BEN is endemic in Bosnia, Bulgaria, Croatia, Romania, and Serbia in settlements around the South Morava River and its tributaries. There is evidence that BEN is an environmentally induced disease.
related to exposure to organic vegetable and/or fungal toxins, especially aristolochic acid, in patients with familial metabolic abnormalities. The disease has an insidious onset and slow progression to terminal renal failure, and patients have an increased incidence of upper tract UC. These tumors are more likely to be low grade and bilateral when compared to those from nonendemic areas, and there is an increased risk of UC after renal transplantation in these patients.

Other Risk Factors. Renal pelvic carcinomas have been reported between 14 and 41 years after thorotrast pyelography. There is also a well-reported association between long-standing chronic infection in the presence of staghorn (struvite) calculi and renal pelvic UC. Chinese herb nephropathy, a chronic tubulointerstitial nephritis related to use of Chinese herbs containing aristolochic acid, is also associated with a high risk of UC, and >50% of these tumors occur in the upper tract. An unusually high incidence of upper tract UC has been reported from endemic areas for “blackfoot disease” of southern Taiwan, due to arsenic contamination of water.

Clinical Features
Gross or microscopic hematuria is the most common presenting symptom for upper tract UC, while there may also be dull flank pain, resulting from gradual onset of outflow obstruction with hydronephrotic distension. Pain may be acute and mimic renal colic due to the passage of blood clot or necrotic tumor fragments. Some patients are asymptomatic at presentation, and the tumor is diagnosed as an incidental finding on radiologic evaluation. Advanced cancers usually present with an abdominal or flank mass, weight loss, anorexia, and bone pain.

Pathology. Diagnosis of upper tract UC is usually made with intravenous urography or retrograde pyelography by detection of a discrete filling defect. Diagnosis is confirmed by cystoscopy and ureteropyeloscopy, with biopsy, while cytologic assessment of washings and brushings from the upper tract may be useful. Only superficial biopsies are performed to avoid risk of perforation due to the thinness of the muscular walls, and therefore, biopsy samples are usually not reliable for staging purposes.

Voided urine cytology is positive in 60% of renal pelvic UC and in 35% of ureteral UC. There is a high positive predictive value for high-grade lesions including CIS, whereas the predictive value for low-grade lesions is <50%. Upper tract cytology specimens can be difficult to interpret as benign cells in this location frequently have an atypical appearance, while lithiasis and inflammation may also result in a false-positive diagnosis. In cases with concurrent bladder UC, there is a possibility of contamination of the upper tract sample.

The morphologic characteristics of urothelial dysplasia and carcinoma of the upper tract are similar to those tumors found in the bladder.

Urothelial dysplasia (low-grade intraurothelial neoplasia) may not be apparent macroscopically, or there may be erythema, erosions, or rarely ulceration. Variable loss of polarity and significant cytologic atypia, not severe enough to merit a diagnosis of CIS, characterize these lesions.

CIS (high-grade intraurothelial neoplasia) is a flat lesion with nuclear anaplasia similar to high-grade UC. This lesion is frequently seen in association with invasive UC, particularly in patients with analgesic nephropathy.

Macroscopically, noninvasive UC may be solitary or multifocal, and there is usually distension of the renal pelvis or ureter (Figs. 4-24 to 4-26). As for bladder UC, papillary
noninvasive tumors are classified as papillary urothelial neoplasm of low malignant potential or papillary UC depending on the architectural abnormalities and the degree of nuclear atypia.

Invasive UC may be solitary or multifocal and are papillary, polypoid, solid nodular (Fig. 4-27), ulcerated, or diffusely infiltrative causing thickening of the renal pelvis or ureter. Infiltration of the renal medulla is preceded by in situ extension of the UC into collecting ducts (Fig. 4-28), and invasive tumors usually form a solid mass involving renal parenchyma, which may mimic a primary renal cell carcinoma (Fig. 4-29). In advanced cases the carcinoma may infiltrate diffusely and often has marked associated desmoplasia (Fig. 4-30). Ureteral tumors may be associated with ureteral obstruction and proximal hydronephroureter (Fig. 4-31).

Invasive UC is classified as low grade or high grade depending on the degree of nuclear atypia and architectural abnormality. As in the bladder, invasion is characterized by suburothelial nests, clusters, or single cells with a stromal reaction and paradoxical differentiation. The stromal reaction can be in the form of retraction artifact, desmoplasia, inflammation, or a pseudosarcomatous reaction. Invasive carcinoma in this location may show the entire morphologic spectrum of bladder UC. Lymph node metastasis from renal pelvic UC is primarily to the renal hilar, paracaval, retrocaval, and paraaortic lymph nodes; from the upper two-thirds of the ureter to the paraaortic, retrocaval, and interaortocaval nodes; and from the lower ureter, to nodes inferior to the aortic bifurcation. Metastatic spread is most commonly to the liver, lungs, and bone, although rare metastatic sites include the heart, skin, and penis.

Cytologic evaluation is not useful in distinguishing papillary from invasive UC as these have similar cytologic characteristics.

High-grade invasive UC, particularly when there is divergent differentiation, can be difficult to differentiate from other invasive carcinomas of the renal pelvis such as poorly...
differentiated SCC and adenocarcinoma. High-grade UC invading into the renal parenchyma can mimic renal cell carcinoma, and in such instances the detection of urothelial CIS or a papillary component can be diagnostically helpful. p63 immunostaining is of value in differentiating UC from renal cell carcinoma as even in poorly differentiated tumors it is positive in 96% of upper tract UC, but not in most renal cell carcinomas. A P A X 8+/p63- immunoprofile supports the diagnosis of collecting duct carcinoma with most UC showing an inverse pattern of staining. Monoclonal antibodies against placental S100 protein (S100P) and GATA3 have also been found useful, as a high percentage of UC is positive, whereas clear cell renal cell carcinomas are negative. CD10 is positive in about 50% upper tract UC, compared to 90% of renal cell carcinomas.

Immunodetection of various antigens has been correlated with outcome for upper tract UC. Uroplakin III staining is found in a high percentage of UC with loss of expression associated with a poor prognosis. Ki-67 overexpression is significantly correlated with tumor grade and stage and is of prognostic value, while p53, matrix metalloproteinase MMP-2, and MMP-9 are of limited value in predicting outcome. The expression of CD44 isoforms is associated with tumor differentiation and progression; however, this is not independent of stage. Alpha-methylacyl-CoA racemase (AMACR) expression may be of prognostic utility, as it is most frequent in high stage and high-grade tumors.

**Morphologic Variants**

**Urothelial Carcinoma with Mixed Differentiation**

UC of the renal pelvis may display divergent differentiation, and a variety of morphologic patterns may be seen in association with UC. Mixed morphologic patterns are present in about 40% of high-grade pelvic UC with the most common subtype...
being SCC (Fig. 4-32), which comprises 10% of cases.\textsuperscript{267,268} Foci of other types of differentiation including adenocarcinoma, sarcomatoid carcinoma, small cell neuroendocrine carcinoma, micropapillary UC, and lymphoepithelioma-like carcinoma may also be present. The median survival for patients with these tumors is <3 years although a small proportion of patients, who present with renal pelvis tumor showing minimal or no infiltration of the renal parenchyma, have a more favorable prognosis following radical nephrectomy (Box 4-2).\textsuperscript{267}

### Microcystic Carcinoma

Rare cases of a deceptively bland variant of invasive UC have been reported in the renal pelvis. In these tumors, there are cysts of varying size lined by single or multiple layers of cuboidal or flattened cells, with minimal cytologic atypia.\textsuperscript{269}

### Micropapillary Urothelial Carcinoma

Micropapillary UC is found in about 3% of UC of the renal pelvis and ureter. These tumors usually present at an advanced stage with lymphovascular invasion and distant metastasis. The presence of invasive micropapillary UC, even focally, appears to indicate a poor clinical course.\textsuperscript{270,271}

### Urothelial Carcinoma with Inverted Growth Pattern

Papillary urothelial neoplasms may show an endophytic growth pattern, and this should be distinguished from true invasion\textsuperscript{272} (Fig. 4-33). In some cases inverted carcinoma extends into the kidney along collecting ducts. These lesions have an excellent prognosis following nephrectomy.\textsuperscript{267}

### Osteoclast-rich Sarcomatoid Carcinoma

Sarcomatoid (undifferentiated) carcinoma containing osteoclast giant cells has been reported in the renal pelvis with associated urothelial CIS and/or high-grade papillary UC. These tumors are composed of evenly spaced multinucleated giant cells on a background of ovoid or spindled mononuclear cells. Multinucleated cells have the morphologic and immunohistochemical properties of osteoclasts being positive for CD68, leukocyte common antigen, CD51, and CD54 and negative for cytokeratins and EMA. These tumors are invariably at a high stage at presentation and have a poor prognosis.\textsuperscript{273,274}

### Urothelial Carcinoma with Choriocarcinoma or Syncytiotrophoblastic Giant Cells

UC with trophoblastic differentiation occurs rarely in the renal pelvis. A close genetic relationship between these two neoplastic components has been documented, pointing to clonal evolution of UC with acquisition of trophoblastic differentiation. In these tumors HCG staining is seen within the choriocarcinoma and focally within the associated high-grade UC. Widespread hepatic and pulmonary metastases with choriocarcinomatous features have been reported with

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**Box 4-2**  
**HISTOLOGIC VARIANTS OF UC SEEN IN THE UPPERTRACT**

<table>
<thead>
<tr>
<th>Variant</th>
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<tbody>
<tr>
<td>UC with squamous differentiation</td>
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<tr>
<td>UC with glandular differentiation</td>
</tr>
<tr>
<td>Micropapillary urothelial carcinoma</td>
</tr>
<tr>
<td>UC with inverted growth pattern</td>
</tr>
<tr>
<td>Osteoclast-rich undifferentiated carcinoma</td>
</tr>
<tr>
<td>Urothelial carcinoma with choriocarcinoma or syncytiotrophoblastic giant cells</td>
</tr>
<tr>
<td>Sarcomatoid variant</td>
</tr>
<tr>
<td>Lipid-cell variant</td>
</tr>
<tr>
<td>Lymphoepithelioma-like carcinoma</td>
</tr>
<tr>
<td>Nested variant</td>
</tr>
<tr>
<td>Plasmacytid variant</td>
</tr>
<tr>
<td>Signet-ring cell</td>
</tr>
<tr>
<td>Clear cell variant</td>
</tr>
<tr>
<td>UC showing rhabdoid differentiation</td>
</tr>
</tbody>
</table>
these tumors. In some cases there are syncyiotrophoblastic giant cells in association with invasive high-grade UC.  

Sarcomatoid Variant  

Sarcomatoid carcinoma (formerly known as carcinosarcoma) is a rare aggressive malignancy composed of epithelial and stromal components. Coexisting UC is present in most cases, and some tumors display heterologous elements. These tumors often coexpress keratins, EMA, and vimentin and usually present with metastatic disease or advanced involvement of renal parenchyma. The prognosis is extremely poor with most patients dying within 2 years.

Lipid-cell Variant  

Rare cases of lipid-cell variant, composed of large epithelial cells with abundant clear multivacuolated cytoplasm mimicking lipoblasts, have been reported in the renal pelvis. Tumor cells lack mucin and are strongly positive for cytokeratins 7 and 20 and EMA. High-grade UC is invariably present. These tumors exhibit aggressive behavior and have a poor prognosis.

Lymphoepithelioma-like Carcinoma  

Carcinoma that histologically resembles lymphoepithelioma-like carcinoma of the nasopharynx and characterized by a heavy lymphocytic or mixed inflammatory infiltrate has been reported in the upper tract. EBV-encoded RNA has not been demonstrated in these tumors, and most are at an advanced stage at presentation.

Other Variants of Urothelial Carcinoma  

Nested, plasmacytoid, signet-ring cell, and clear cell variants of UC, as well as tumors showing rhabdoid differentiation, rarely occur in the renal pelvis and ureter.

Prognosis and Predictive Factors  

Tumor stage and grade are the most significant factors predicting recurrence and survival. The pT3 stage for renal pelvic UC differs from that of the ureter based on anatomical differences and includes invasion of the renal parenchyma. Involvement of renal tubules without stromal invasion in renal pelvic tumors should not be considered pT3. Patients with pT3 tumors, who have macroscopic or extensive renal parenchymal and/or fat infiltration, appear to have a worse prognosis than those with pT3 tumors displaying only microscopic invasion of these areas. In some studies, the prognosis of these tumors was found to be similar to pT4 cancers. There appears to be no significant difference in the stage-specific 5-year survival for renal pelvic and ureteral UC. Although upper tract tumors usually present at a higher stage than bladder UC, they have a similar behavior to bladder UC of the same stage and grade. The overall 5-year disease-specific survival of patients diagnosed with an upper tract UC has improved over the last 45 years and currently is about 75%. Atrialar 5-year disease-specific survival rates by the primary tumor stage are 95% to 100% for Ta/CIS, 85% to 92% for T1, 75% to 83% for T2, and 40% to 60% for T3. Patients with stage 4 tumors have a very poor prognosis with a median survival of 6 months. The ISUP/WHO grading system for bladder UC, incorporated in the 2004 WHO classification of bladder tumors, is also applied to UC of the upper tract and has prognostic significance. Other independent prognostic factors are patient age, sex, race, type of surgical procedure, tumor multifocality, and vascular invasion.

Patients with upper tract UC are at risk of developing synchronous or metachronous tumors in other urothelial locations, including the contralateral upper tract. Ipsilateral upper tract recurrence is common in patients managed without nephroureterectomy, and one-third of patients with UC have an upper tract relapse, following percutaneous or ureteroscopic tumor resection, or ablation. The risk of relapse is grade dependent as <20% of low grade tumors relapse, which compares with >50% of high grade tumors. Between 20% and 50% of patients with upper tract carcinoma subsequently develop bladder UC, and in particular, those with locally resected tumors require lifelong surveillance.

Treatment  

Open or laparoscopic radical nephroureterectomy or distal ureterectomy for distal ureteral tumors is the standard treatment for all but the lowest risk tumors. Endoscopic resection may be undertaken for small low-grade tumors, while BCG and interferon alpha 2B after tumor ablation have also been found effective for papillary tumors. Adjuvant radiotherapy, with and without concurrent chemotherapy, after tumor resection has been found by some to be beneficial for locally advanced cancers; however, others have found that these therapies do not affect the outcome of patients with advanced disease. Surgery and subsequent adjuvant chemotherapy, with paclitaxel and carboplatin for locally advanced high-risk upper tract cancers, have shown a reduced risk for the development of distant metastases.

Squamous Cell Carcinoma  

SCC accounts for 0.5% of renal tumors and 6% to 15% of upper tract malignancies. Most SCC of the upper tract is associated with chronic infection, renal calculi of long duration, and outflow obstruction with hydroureter. A history of urolithiasis is found in 25% of patients with SCC of the renal pelvis, and it is presumed that chronic irritation and inflammation promotes neoplastic transformation. A history of abuse of analgesics containing phenacetin produces a risk of SCC higher than that of UC. Occasionally SCC is related to a history of external beam radiotherapy to the abdominal or pelvic region. These tumors have been associated with paraneoplastic syndromes such as hypercalcemia, leucocytosis, and thrombocytosis.

The age distribution of patients with SCC of the upper tract is similar to that seen with UC, with a median age at presentation of 72 years. These tumors are more frequent in females in contrast to UC of the upper tract and bladder. Common presenting symptoms are hematuria and flank pain. Radiologic
findings are nonspecific, and solid space-occupying lesion, hydronephrosis, and calcification are common.

Typically, SCC is large and unifocal within the renal pelvis or ureter and frequently involves the kidney and perinephric tissues.

Histologically these tumors typically have a solid or mixed solid and papillary pattern, while other microscopic features are similar to SCC seen in other locations, although upper tract tumors are typically high grade.

Metastatic SCC from another location, such as lung, needs to be considered in the differential diagnosis and may require clinical investigation for exclusion. UC with squamous differentiation, rather than SCC, is diagnosed when there is any associated UC including urothelial CIS.\(^{267}\) This is of little practical importance, however, as there is no significant difference in prognosis between patients with pure SCC and those with focal areas showing other histology, including UC.

Tumor stage, but not grade, appears to have strong prognostic value, as most tumors present at an advanced stage. Compared with 62% of UCs, <5% of SCCs are at stage pT2 or lower at diagnosis; however, there is no significant difference in the disease-specific 5-year survival rates between patients with SCC and UC of the same stage.\(^{268,269}\) The outcome for patients with advanced upper tract SCC is poor with a mean survival in the order of a few months. Bladder SCC and metachronous contralateral upper tract tumors following surgery for an upper tract SCC are more unusual than with upper tract UC, and for this reason the value of regular cystoscopy and follow-up urography after an upper tract SCC is questionable.

Vascular invasion, solid tumor growth pattern, and large tumor size have prognostic significance, and the most common metastatic sites are the regional lymph nodes, lungs, liver, and bone.

Patients with stage T1 to T2 SCC can be treated with radical surgery, and these have a good prognosis. A dvanced tumors respond poorly to adjuvant or neoadjuvant chemotherapy and radiotherapy.\(^{268}\)

**Adenocarcinoma**

A denocarcinoma of the upper tract is rarely seen and accounts for <1% of renal pelvic tumors. Males and females are equally affected, and predisposing factors include chronic irritation, repeated infections, nephrolithiasis, pyleoureteral glandularis, and urothelial glandular (intestinal) metaplasia.\(^{267}\) Typically, patients present with gross or microscopic hematuria, or flank pain.

Hydronephrosis, with distension of the renal pelvis or the involved segment of ureter, with copious thick viscid mucus, is a typical finding.\(^{267}\) A denocarcinomas, particularly those in elderly patients, may be of the intestinal type and can show tubulovillous, mucinous (Fig. 4-34), clear cell, and signet-ring cell varieties. Nonintestinal papillary adenocarcinomas account for 7% of adenocarcinomas. These occur in a much younger patient population and are characterized by the presence of psammoma bodies.\(^{267-269}\)

Metastatic adenocarcinoma, collecting duct carcinoma, and UC with glandular differentiation need to be considered in the differential diagnosis. Nonintestinal-type adenocarcinoma, which has been postulated to be of collecting duct origin, is differentiated from Bellini duct carcinoma by its almost entirely renal pelvic location, minimal cytologic atypia, and the presence of frequent psammoma bodies. Absence of atypia and proliferation in adjacent collecting ducts are also helpful feature in differentiation.

Survival of patients with upper tract adenocarcinoma depends on histologic subtype, histology grade, and tumor stage at presentation. Tubulovillous adenocarcinomas are the most aggressive subtype of adenocarcinoma with a 5-year survival rate of <30%. In comparison, mucinous tumors have a 5-year survival rate of 67%, while that of papillary nonintestinal tumors approaches 100%.\(^{267}\) Nephrectomy or nephroureterectomy is beneficial for lower-stage tumors, although most adnocarcinomas are high grade and present at a high stage\(^{266,268}\) and chemotherapy and/or radiotherapy may improve short-term survival.

**Small Cell Carcinoma**

Primary small cell carcinoma of the renal pelvis and ureter is very rare and usually presents at an advanced stage.\(^{266,310,311}\) These tumors occur in an age group similar to that of UC, with a median age at presentation of 62 years. There is a female predominance (male to female ratio 1:3.4), and the most common presenting symptoms are abdominal pain and hematuria. Distant metastases are present in 32% of patients at the time of diagnosis.\(^{311}\)

Most small cell carcinomas are large at presentation and have gross and microscopic features similar to those of small cell neuroendocrine carcinomas from other locations. Neuroendocrine markers such as CD56, chromogranin A, synaptophysin, and neuron-specific enolase (NSE) are usually positive.

As with small cell neuroendocrine carcinoma in other locations, these tumors have propensity to spread via the lymphatics and blood vessels and to infiltrate to lymph nodes and distant organs, and death usually occurs within 1 year of diagnosis.\(^{311}\) Surgery and systemic chemotherapy are the primary therapeutic modalities for small cell carcinomas, and
the use of platinum-based chemotherapy has been shown to improve overall survival.311

Carcinoid Tumor
Carcinoid tumors have rarely been reported from the ureter and renal pelvis. These tumors usually occur in patients younger than 50 years of age, and males and females are equally affected. Carcinoïd syndrome has not been reported in association with these tumors, and patients frequently present with lymph node metastases. Despite the presence of distant metastases, these tumors often have a prolonged clinical course.314

Upper tract carcinoids have morphologic features similar to those of carcinoid tumors occurring elsewhere, and cytochemical examination of urine sediment may occasionally be diagnostic.315 These tumors are positive for pancytokeratin, synaptophysin, vimentin, chromogranin, and NSE and contain dense core granules on ultrastructural examination.313-315

Mesenchymal Tumors: Benign
Leiomyoma
Despite being the most commonly reported benign mesenchymal neoplasms of the ureter and renal pelvis, upper tract leiomyomas are rarely seen. These tumors are usually found in adults with an average age at presentation of 44 years, although occasional cases have been reported in children.316-318

The clinical presentation of these tumors is variable, and although most are asymptomatic and discovered incidentally, others present with flank pain, hematuria, upper quadrant mass, outflow obstruction, or hydronephroureter.316

Grossly, leiomyomas are well-circumscribed whorled white tumors and may be polypoid, with histologic features similar to those of leiomyomas in other organs. Mitotic figures are rare (<2 per 10 high-power fields),319 and occasionally tumors with cellular atypia resembling bizarre (symplastic) leiomyoma of the myometrium are seen.319

Upper tract leiomyomas usually express one or more smooth muscle markers (desmin, muscle-specific actin; MSA and SM SA), but unlike renal capsular leiomyomas are negative for HMB 45.320

Hemangioma
Rare cases of sporadic hemangioma have been reported in the upper tract, in both adults and children.321,322 While multiple renal pelvic hemangiomas may occur as part of the Klippel-Trenaunay-Weber syndrome.323

These tumors typically present with massive hematuria, usually necessitating nephrectomy. Renal pelvic lesions may cause UPJ obstruction and hydronephrosis, while pericaval hemangiomas can result in renal papillary necrosis.324 Histologically upper tract hemangiomas can show a cavernous, capillary, or fibrous morphology.

Neurofibroma
Neurofibromas rarely occur in the renal pelvis.325 Segmental neurofibromatosis and solitary neurofibroma involving the ureter have also been reported.326,327 These tumors may occur sporadically or may be a manifestation of von Recklinghausen neurofibromatosis. Patients present with flank pain and a mass lesion is usually found on radiologic investigation.327 The pathologic features of upper tract neurofibroma are similar to those seen in other locations.

Other Tumors
Hemangiomyoma of the ureter has been reported in a child.328 Periureteric lipoma and benign schwannoma,330 causing extrinsic UPJ obstruction, and hibernoma331 are also rare tumors reported in this location.

Mesenchymal Tumors: Malignant
Leiomyosarcoma
Leiomyosarcomas arising in the renal pelvis are rare. These tumors occur in adults and are more common in females. They usually present at a relatively late stage with gross hematuria322-334 and patient age and stage at diagnosis are the strongest predictors for survival. Overall survival for leiomyosarcoma in this location is similar to that of UC.333

Rhabdomyosarcoma
Rhabdomyosarcoma of the renal pelvis is extremely rare. Botryoid-type pleomorphic rhabdomyosarcoma and embryonal rhabdomyosarcoma, producing a polypoid mass attached to the renal pelvis, have been reported in adults and children.336

Other Tumors
Rare cases of ureteral angiosarcoma have been reported, with a case described in a long-term functional renal allograft.337,338 Botryoid nephroblastoma of the renal pelvis and ureter, with limited parenchymal involvement, occurs rarely in the pediatric age group.339,340 These patients present with a flank mass, low-grade fever, abdominal pain, and gross hematuria. Radiology displays renal enlargement, with typically a heterogeneous mass occupying a dilated pelvicalyceal system and ureter. Malignant peripheral nerve sheath tumors rarely occur in the renal pelvis.341 Ewing sarcoma/primitive neuroectodermal tumor is a highly malignant tumor and has a poor prognosis.342 A nontobosh malignant mesenchymal tumor reported in the renal pelvis is malignant fibrous histiocytoma, which is an extremely aggressive neoplasm, with little response to radiotherapy and chemotherapy.343

Primary malignant melanoma of the renal pelvis occurs in both adults and children.344,345 These tumors are composed of large eosinophilic cells, but are rarely of clear cell type. Melanoma in this location is more commonly metastatic and is usually part of a disseminated process.
Hematopoietic and Lymphoid Tumors

Lymphomatous involvement of the upper tract usually occurs in association with systemic disease, or renal or retroperitoneal lymphoma. Rare cases of non-Hodgkin lymphoma involving the ureter and renal pelvis have been reported, and lymphomatous infiltration of the ureter is an uncommon cause of ureteral obstruction.

Obstructive nephropathy may result from granulocytic sarcoma (chloroma) arising within the renal pelvis. Ureteral obstruction due to an isolated focus of chronic lymphocytic leukemia has also been reported. In a patient with a history of leukemia, this possibility needs to be considered in the differential diagnosis of urinary obstruction, even in the absence of other evidence of active disease, as the treatment is nonsurgical.

Plasmacytoma involving the kidney and renal pelvis is a rare manifestation of extramedullary plasmacytoma. While these tumors may be part of multiple myeloma, in rare cases the neoplastic plasma cell proliferation has been confined to the renal pelvis, hilar region, and renal capsule.

Secondary Tumors

The majority of ureteropelvic metastatic tumors are of nonurologic origin and occur as part of widespread dissemination. Reported metastatic tumors include testicular seminoma, colonic, rectal and gastric adenocarcinoma, pulmonary carcinoma, breast carcinoma, cutaneous melanoma, renal cell carcinoma, and tumors of pelvic organs.

STAGING

The TNM clinical classification of the American Joint Committee on Cancer (AJCC)/Union Internationale Contre Le Cancer (UICC) is the most commonly employed staging system for tumors of the renal pelvis and ureter (Table 4-3). The thickness of the suburothelial stroma and muscularis varies in the calyces, the renal pelvis, and the ureter and may cause difficulties in staging of tumors. Further, staging of large and often friable pelvicalyceal tumors can be difficult, particularly if the tumor is poorly fixed. Large papillary

<table>
<thead>
<tr>
<th>Table 4-3</th>
<th>TNM CLASSIFICATION OF CARCCINOMAS OF THE RENAL PELVIS AND URETER</th>
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<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td><img src="8b75ad8485e1f0ad3687a4b38c60f200.png" alt="Table" /></td>
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<tr>
<td><strong>Regional Lymph Nodes (N)</strong></td>
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</tr>
<tr>
<td><strong>Distant Metastasis (M)</strong></td>
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</tr>
<tr>
<td><strong>Stage Grouping</strong></td>
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tumors in this location may have a prominent endophytic growth pattern and appear to push into renal sinus fat. This raises the possibility of misinterpreting these tumors as invasive carcinomas. Pagetoid spread of UC into renal parenchymal invasion. It should also be noted that tubular spread of carcinoma without invasion remains an in situ process, in contrast to renal parenchymal invasion, which is classified as pT3 disease. Unlike tumor showing renal parenchymal invasion, tumor confined to the renal tubules maintains a renal tubular contour and there is no stromal reaction.357

**SPECIMEN HANDLING**

Appropriate handling and assessment of specimens is necessary for accurate diagnosis and evaluation of prognostic features and is crucial for appropriate patient management.358 Surgical specimens must be accompanied by adequate clinical history of urologic and nonurologic disease, including information regarding previous treatment.

**Biopsy**

Biopsy is obtained with cold cup forceps, diathermy forceps, or small diathermy loops. These must be transferred to formalin with minimal handling. The entire biopsy specimen must be submitted for processing and multiple sectioning. Given the thinness of the wall and relative inaccessibility of the upper tract, ureteral and pelvocalyceal biopsies are typically small and superficial, sometimes displaying crush artifact. Therefore, these may be suboptimal for assessment, which may prevent definitive diagnosis. This can also prevent accurate assessment of the grade and pathologic stage of tumors from this location.

**Nephro-ureterectomy**

Frozen section of ureter resection margins may be requested. Longitudinal sections or a cross section of the inked ureter margin may be examined.

For nephro-ureterectomy specimens dissection is best commenced at the renal hilum following identification of the ureter, renal artery, and renal vein. The ureteral and hilar soft tissue margins are inked, and a cut, beginning in the renal pelvis, is extended to bivalve the kidney and then extended through the perinephric fat and down the ureter. The location of any tumor within the pelvocalyceal system or ureter is recorded, along with a description of the macroscopic features, dimensions, depth of invasion, involvement of renal parenchyma, renal sinus, perinephric fat, hilar lymph nodes, and blood vessels, and distance from the surgical resection margins. Photographs of the opened specimen are desirable. Tissues demonstrating the tumor and its relationship to renal parenchyma and peripelvic/perireteral soft tissue are submitted for histology. Separate sections of the resection margins (ureteral, closest hilar soft tissue, and perinephric) and representative sections of nonneoplastic kidney, renal pelvis and ureter, renal sinus, hilar lymph nodes (if present), and hilar blood vessels are also taken.

**Ureterectomy**

The cut margins are inked and both ends are submitted for separate evaluation. The entire ureter is then opened, and careful inspection of the ureteral mucosa and wall is undertaken. Any tumor is identified and the distance to the resection margins is recorded along with the macroscopic level of invasion and involvement of perireteral soft tissues. Several blocks of the tumor are submitted, and these should include the closest approach to the perireteral soft tissue margin.

**REPORTING**

College of American Pathologists guidelines should be used in reporting (Box 4-3).

<table>
<thead>
<tr>
<th><strong>Box 4-3</strong></th>
<th><strong>COLLEGE OF AMERICAN PATHOLOGISTS GUIDELINES</strong></th>
</tr>
</thead>
</table>
| **URETER, RENAL PELVIS: Biopsy** | Specimen
| | Specimen Laterality
| | Histologic Type
| | Associated Epithelial Lesions
| | Histologic Grade
| | Tumor Configuration
| | Adequacy of Material for Determining T Category
| | Microscopic Tumor Extension
| | Pathologic Staging (pTNM)
| | Additional Pathologic Findings
| **RENSAL PELVIS: Resection/Nephro-ureterectomy, Partial or Complete** | Procedure
| | Specimen Laterality
| | Tumor Size
| | Histologic Type
| | Associated Epithelial Lesions
| | Histologic Grade
| | Microscopic Tumor Extension
| | Tumor Configuration
| | Margins
| | Lymphovascular Invasion
| | Pathologic Staging (pTNM)
| | Additional Pathologic Findings
| | Pathologic Findings in Non-neoplastic Kidney
| **URETER: Resection** | Procedure
| | Specimen Laterality
| | Tumor Size
| | Histologic Type
| | Associated Epithelial Lesions
| | Histologic Grade
| | Microscopic Tumor Extension
| | Tumor Configuration
| | Margins
| | Lymphovascular Invasion
| | Pathologic Staging (pTNM)
| | Additional Pathologic Findings
Biopsy

The biopsy report should record the tissues present. In case of malignancy, tumor type, and ISUP/WHO grade, the extent of invasion into the different layers and presence of vascular, lymphatic, and perineural invasion must be recorded. It is also important to report the adequacy of the specimen and the presence of any urothelial denudation.

Nephro-ureterectomy

The histologic report of nephroureterectomy specimens should contain a description of the location, size, morphologic features, grade, and stage of tumor, detailing the extent of invasion into the layers of the renal pelvic or ureteral wall. Any tumor should be recorded in addition to the histologic type, the location, size, and distance to resection margins of any phatic and perineural invasion, and adequacy of resection.

Parenchyma and renal sinus, the presence of vascular lymphatic, and perineural invasion must be recorded. It is also important to report the adequacy of the specimen and the presence of any urothelial denudation.

Ureterectomy

The location, size, and distance to resection margins of any tumor should be recorded in addition to the histologic type, grade, and extent of invasion into the different layers. Any vascular, lymphatic, and perineural invasion should be noted along with an assessment of the completeness of resection.

References


