The following table lists the most common tumor-like lesions of the urinary bladder:

Epithelial abnormalities:
- Von Brunn’s nests
- Cystitis glandularis
- Cystitis cystica
- Squamous metaplasia
- Nephrogenic adenoma
- Papillary hyperplasia

Non-specific cystitis
- Papillary-polypoid cystitis

Specific cystitis
- Follicular cystitis
- Interstitial cystitis
- Eosinophilic cystitis
- Giant cell cystitis
- Radiation cystitis
- Incrusted cystitis
- Emphysematous cystitis
- Granulomatous cystitis

Malakoplakia

Polyps:
- Fibroepithelial
- Other

Amyloidosis

Müllerian lesions including endometriosis, endocervicosis, and müllerianosis

Postoperative spindle cell nodule

Inflammatory pseudotumor

Ectopic prostate

Paraganglionic tissue

From all the above, I will focus on the ones that more often may cause problems in differential diagnosis with malignant tumors involving the urinary bladder, mostly related to transitional cell carcinoma.
CYSTITIS GLANDULARIS

This lesion evolves and imperceptibly merges with Von Brunn’s nests, a common epithelial abnormality of the bladder. When these nests become cystic with central lumen formation and polarization of the inner most cells, the term cystitis glandularis is used. Cystitis glandularis is a relatively common histologic finding, most frequently seen in the trigone as seen in Von Brunn’s nests. It is divided into:

a) Usual type
b) Intestinal type

On cystoscopic examination, these lesions may be seen as a nodular or polypoid growth, especially in cases of cystitis glandularis of intestinal type, mimicking on occasion a malignant neoplasm. On microscopic examination, cystitis glandularis, of the usual type, is composed of an inner layer of columnar to cuboidal cells surrounded by an outer layer/s of transitional cells. Similar epithelium may be present on the surface. Cystitis glandularis of the intestinal type is less frequent (incidence of 0.1-0.9%) and more commonly seen in patients with extrophy and pelvic lipomatosis. The glands are lined by mucinous epithelium including goblet cells, closely resembling colonic epithelium. It may be very florid and associated with mucin extravasation. The stroma may show mild edema or hyalinization and inflammatory infiltrate. Young & Bostwick reported 6 of such lesions that caused serious problems of differential diagnosis with mucinous adenocarcinoma of the bladder. Five out of the 6 patients had a gross abnormality, thought to be consistent with a neoplasm, in the region of the trigone or bladder neck under cystoscopy. On microscopic examination, numerous glands were present in the lamina propria, some had the appearance of cystitis glandularis of the usual type; however, most of them were lined by tall columnar epithelial cells, including goblet cells without surrounding transitional type cells. This intestinal type epithelium was also seen lining the surface of the bladder. On closer examination, the glands had basally located nuclei without any significant degree of cytologic atypia. Paneth cells could also be found. Extravasated basophilic mucin was present in the stroma in all, and in four cases this finding was conspicuous, however, no intestinal epithelium was seen floating in the extracellular mucin.

The differential diagnosis includes:

**Bladder adenocarcinoma.** This is frequently of intestinal type. The distinction between these two entities is based on architecture and cytology. The benign process is characterized by an orderly distribution of glands lacking cytologic atypia and absence of mucinous cells free floating in mucinous pools.

**Urachal adenocarcinoma.** This type of adenocarcinoma may be low grade, paucicellular, and show extensive mucin extravasation, and thus, it may be difficult to make the diagnosis of malignancy in a small specimen. It is important to remember that urachal lesions are typically located in the anterior aspect of the bladder dome while cystitis glandularis is located in the trigone or bladder neck.
**Secondarily involvement by large bowel colloid carcinoma.** The distribution of disease is helpful as the bulk of the tumor is present in the serosa and muscularis propria with much less involvement of the lamina propria and mucosa and the degree of cytologic atypia is marked at least focally. Patients also have clinical symptoms and signs related to the main tumor.

**Endocervicosis.** Benign müllerian lesion composed of glands lined by endocervical type epithelium, some of which may rupture resulting in mucin extravasation. However, the latter if present is very focal and associated with histiocytic and fibroblastic inflammatory response. Furthermore, endocervicosis is centered in the muscularis propria.

Finally, it should be noted that there is controversy regarding the malignant potential of cystitis glandularis of intestinal type. Over the years it has been stated that diffuse intestinal metaplasia is associated with an increased risk of bladder carcinoma, as intestinal metaplasia often coexists with adenocarcinoma. However, Corica and colleagues collected a series of 53 patients with intestinal metaplasia and long follow-up (approximately 14 years). They concluded that intestinal metaplasia was not a strong risk factor for adenocarcinoma of the bladder.

**NEPHROGENIC ADENOMA**

This is a rare benign lesion of the urothelium, first described by Davis in 1949, but characterized in detail by Friedman and Kuhlenbeck in 1950. The term nephrogenic adenoma (NA) was coined because of the morphologic similarity of the lesion to the distal nephron. Predisposing factors include genitourinary trauma, surgery, mechanical irritation, chronic inflammation, and renal calculi. Nephrogenic adenoma has also rarely described in bowel conduits. The lesion also has been noted in immunosuppressed patients, especially those with a transplanted kidney. Some authors prefer the term nephrogenic metaplasia, as this lesion was initially thought to arise from a metaplastic process. More recently, it has been shown that at least a subset of NAs that develop in patients with a kidney transplant derive from renal tubular cells that implant in the bladder mucosa as NAs in female recipients of transplants from male donors and male recipients of transplants from female donors showed the same sex-chromosome status as the donor kidney, but not the same sex-chromosome status as the recipient’s surrounding bladder tissue. The rationale behind these findings is that in renal diseases and hypoxic conditions, including immunosuppression, there is an increased detachment of viable renal tubular cells that secondarily seed, implant, and grow in the urothelial mucosa. However, the origin of NA in non-immunocompromised patients is still unclear, as there is some type of injury related to most NAs, and consequently, these lesions could also have a similar pathogenesis.

The lesion occurs mainly in adults, where it is more common in males, but the reverse pertains to children. Approximately 80% of the lesions occur in the bladder, with the remainder involving the urethra (15%) or ureter (5%) and, rarely, the renal pelvis. In most cases, it is an incidental finding, but in 1/3 of the cases, the lesions are sizable and 10% are 4 cm or even larger. In those cases, it may be potentially confused with a malignant tumor, most commonly a low-grade papillary transitional cell carcinoma.

On **microscopic examination**, NAs may show tubular or tubulocystic, papillary, and, much less frequently, solid growth. The tubular pattern is the most common, present in 96% of cases in the
largest review of NAs (80 cases). The tubules frequently grow in a band-like pattern with a sharp demarcation from the underlying stroma. The tubules vary in size and shape, and although the majority are small and contain either basophilic or eosinophilic secretions, on rare occasions the tubules may be solid. An appreciable basement membrane may be seen surrounding some of the tubules. The cysts are frequently admixed with the tubules but in most cases are not really conspicuous. The papillary pattern has an exophytic growth in most cases, but it can be endophytic. The papillae do not branch and it is very rare to see this component in the absence of tubules. The final and least common pattern is solid, and when present typically represents a minor component of the lesion. Of note, the tubules of NA may be intermixed with muscle fibers of the muscularis mucosa in the bladder, ureter, or, more often, with the muscle fibers present in the wall of the prostatic urethra. In these cases, the specimens are more often obtained by transurethral resection. The cells that line the tubules, cysts, and papillae are cuboidal to columnar to flattened with scant eosinophilic to slightly clear and granular cytoplasm. Hobnail cells are typically present, most often lining the cysts, but are rarely conspicuous. Cells lining tiny tubules have a compressed nucleus with a single vacuole containing basophilic material resembling signet-ring cells. The nuclei are round to oval with minimal cytologic atypia. Nucleoli are inconspicuous and mitoses rare (<1/10 high power fields). In the largest study of 80 NAs, mitotic activity was only seen in 5% of the lesions. The term “atypical NA,” introduced by Cheng and colleagues, identifies lesions characterized by severe cytologic atypia, including nuclear enlargement, nuclear hyperchromasia, and enlarged nucleoli. One of these features, prominent nucleolus, was also observed at least focally in 16 NAs in the largest published series, and in 14 out of 26 NAs involving the prostatic urethra in another series. The stroma associated with NA is focally edematous and contains variable amounts of inflammatory cells. Stromal calcification may be seen. It is not unusual that NA is seen in association with other reactive benign lesions of the bladder, including cystitis glandularis, polypoid cystitis or squamous metaplasia. A recently described variant of NA is the so-called ‘fibromyxoid nephrogenic adenoma,’ where there is a predominance of spindle cells within a fibromyxoid background. However, in all these cases, the classic tubular pattern is also present. It is always important to be aware of this rare morphology of nephrogenic adenoma and particularly when there is any history that may have elicited this peculiar process diligent search for the more characteristic patterns of this lesion.

The immunohistochemical profile of NA is characterized by diffuse positivity for wide spectrum keratins, CK 7, EMA, vimentin, and PAX2 (an antigen found during nephrogenesis) and PAX8. Different types of lectins are expressed, as seen in renal tubular epithelium. There is frequent staining for CA-125 as well as focal positivity for CEA, CK 20, CD10, and, in some cases, for RCC antibody. Kidney-specific cadherin (KSP-CAD) is a recently characterized calcium-dependent cell adhesion molecule that appears to be kidney-specific in its distribution, with expression localized primarily in the distal nephron. We have stained 10 NAs and all were negative for this antibody. Aquaporin 1 (marker of the proximal and descending thin limb of Henle’s loop renal tubular cells) has been shown to be positive in one study of NAs in immunosuppressed patients. However, in our experience, most NAs in patients without known immunosuppression are negative for aquaporin 1, whether by immunohistochemistry or immunofluorescence; thus, it is still unclear whether the origin of these lesions is related to the proximal nephron, at least in non-immunocompromised patients. Nephrogenic adenoma does not show the typical membranous/luminal staining for uroplakin as seen in transitional epithelium,
and the immunohistochemical profile just described raises questions about the metaplastic nature of NA overall. It is important to be aware that P50S (AMACR), which is an enzyme normally present in the mitochondria of renal tubular epithelium and hepatocytes but absent or minimally expressed in benign prostatic glands and urothelium, is expressed in NAs, including those involving the prostatic urethra. NAs are negative for p63 and may not express 34BE12 increasing further the confusion with prostatic adenocarcinoma. It is noteworthy that the finding of AMACR and 23BE12 in renal tubules would support the hypothesis that NA may have a renal origin. Finally, one recent study has reported focal weak positivity for PSA and PSAP in some cases. This overlapping profile highlights the importance of clinicopathologic correlation and careful histologic examination, and demonstrates the importance of using a panel of antibodies in differentiating these tumors through immunohistochemistry. Recently, S100 has been shown to be helpful in this differential diagnosis. A strong and distinct cytoplasmic or nucleocytoplasmic staining of S100A1 was found in 17 out of 18 cases of nephrogenic adenoma (94%), but never in prostatic adenocarcinoma. p53 and Ki-67 expression are typically negative in NAs. Ploidy analyses have shown that these lesions are typically diploid, while cytogenetic studies have shown that NA cells are characterized by monosomy 9.

The differential diagnosis includes:

**Clear cell carcinoma (CCC).** This is probably the most common and most difficult problem in differential diagnosis with NA and may arise in biopsy specimens where there is only a small amount of sampled lesion. Clear cell carcinoma is more frequently seen in older women. Patients with these tumors frequently present with hematuria or other clinical symptoms, and the tumors often form a visible mass. On microscopic examination, the histologic patterns of CCC overlap with those seen in NA, although a solid growth is more common. The papillae tend to branch and they may contain hyalinized fibrovascular cores, as seen in CCCs of the female genital tract. Clear cell carcinoma and NA also share the presence of clear and hobnail cells. However, the degree of cytologic atypia and mitotic activity seen in CCC is by far more conspicuous than in NA. Clear cell carcinoma may have a subtle appearance focally; however, the presence of any degree of cytologic atypia or mitotic activity should alert any pathologist, who should be very cautious in making a benign diagnosis. Furthermore, CCC frequently shows areas of hemorrhage and necrosis and infiltrates deep into the vesical wall. Both lesions may arise in association with a diverticulum, especially when located in the urethra. It has been postulated by some investigators that NA may be the precursor lesion of CCC; however, this theory has never been proven. Immunohistochemical stains are not helpful in this differential diagnosis, as the lesions show an overlapping immunohistochemical profile, including positive staining for low-molecular weight keratins, CK7, CK20, PAX2, and PAX8 and negative staining for estrogen and progesterone receptors, PSA, and PSAP.

**Bladder cancer with prominent nested or tubular growth patterns.** Helpful features in this distinction include more than one cell layer lining the tubules in cases of bladder cancer (typical of urothelium but not NA); the presence of more appreciable cytologic atypia; and the absence of other patterns typically seen in NA, as well as the invasion into the muscularis propria seen in some carcinoma cases. Immunohistochemically, the nested variant of urothelial carcinoma shares some features with high-risk conventional urothelial carcinomas, such as high proliferation index, and with rare exceptions, this feature contrasts with the absence of Ki-67 expression in
most NAs. Nevertheless, p53 immunoreactivity is not frequently seen and cannot be used in this differential diagnosis. Of interest, recent studies have revealed that NA shows the same chromosomic aberrations as superficial bladder cancer, though to a smaller extent.

**Prostate adenocarcinoma** may enter into the differential diagnosis in those cases where NA involves the prostatic urethra as mentioned earlier. Tubules of NA may show a pseudoinfiltrative growth, intercalating between muscle fibers. Furthermore, the cells lining the tubules may show nuclei with prominent nucleolus, and mucinous secretions may be present in the lumens of the tubules. In these cases, it is important to keep in mind the possibility of NA before making the diagnosis of prostate cancer. Immunohistochemical stains for p63, 34\(\beta\)E12 and P504S are not helpful in this differential diagnosis in many instances, and it seems that compared to bladder NAs, urethral NAs express AMARC more often. However, PSA and PSAP are helpful in most cases, as prostatic adenocarcinoma typically shows diffuse and strong positivity, in contrast to the weak and focal positivity seen in some NAs. Most importantly, the tubular pattern is associated with other typical architectural patterns of NA, the cytologic atypia is frequently of degenerative type, and no mitotic figures are found. Finally, the presence of acute or chronic inflammatory cells is not a feature of prostate cancer, whereas it is typically present in NAs.

**Signet ring cell carcinoma of the bladder or metastatic to the bladder** very rarely may enter into the differential diagnosis, especially when the most prominent pattern is that of very small tubules containing basophilic secretion. This growth is always accompanied by larger tubules and neither shows diffuse involvement of the bladder wall nor the cytologic atypia seen in signet ring cell carcinoma.

Nephrogenic adenoma may recur, and the recurrence rate ranges from 28 to almost 90%, but there is no proof that NA may undergo malignant transformation.

**POLYPOID/PAPILLARY CYSTITIS**

These lesions are the result of inflammation and edema in the lamina propria. The term polypoid is used for bulbous, broad-based lesions and the term papillary for lesions with a finger-like appearance. The former is by far more common. Polypoid cystitis is more frequently seen in men and it is present in up to 80% of patients with indwelling catheter. Vesical fistulae, whether resulting from appendicitis, Crohn disease, diverticulitis or colorectal cancer, are also frequently associated with polypoid cystitis. However, in about 50% of patients, obvious signs of extravescical disease may be initially absent making the diagnosis more difficult. Most lesions are microscopic in size, but in up to 33% may reach 5 mm in largest dimension. On cystoscopy, the appearance of the lesions not infrequently suggests the possibility of bladder carcinoma. On microscopic examination, the main problem is to distinguish polypoid/papillary cystitis from papillary urothelial carcinoma, but on low-power examination in contrast to papillary transitional cell carcinoma, the fronds are much broader and branching is absent or minimal. There is prominent edema associated with inflammatory and metaplastic changes such as squamous metaplasia. On high-power examination, although the urothelium is hyperplastic, it is not by far to the degree seen in papillary transitional cell carcinoma and umbrella cells are more commonly found in these benign urothelial lesions. Finally, polypoid cystitis does not have cytologic atypia, other than that associated with inflammation.
REACTIVE ATYPIA INCLUDING RADIATION INDUCED ATYPIA

These are lesions that may cause problems in differential diagnosis on clinical examination but mainly under the microscope. Patients obviously have a previous history of radiation, not necessarily for bladder cancer, but for prostate or cervical cancer, in some instances forgotten. **Cystoscopy** may show small papillary lesions, slight mucosal irregularities or be non-specific. On **microscopic examination**, the earlier changes appear after 3 to 6 weeks and include acute cystitis and desquamation of the urothelial cells associated with hyperemia. Later, there is epithelial hyperplasia producing a pseudoinfiltrative appearance with some nests being jagged and others having rounded contours. Budding off single cells may also be seen, and the nests may show squamous differentiation, all those features raising the suspicion of a malignant process. These cells show mild to severe cytologic atypia with nuclear hyperchromasia, however, nucleoli are inconspicuous, the nuclear/cytoplasmic ratio is preserved or increased in most cases and mitotic figures are typically absent, features that are not characteristic of a malignant process. Other helpful features are the finding of scattered enlarged fibroblasts in the lamina propria associated with nuclear hyperchromasia, hemorrhage and or fibrin deposition, edema, inflammatory cells and ectatic vessels, some of them showing myointimal thickening and eccentric accumulation of amorphous pink material, all these features being highly suggestive of a reactive lesion. The **immunohistochemical profile** of radiation induced atypia, even when marked, typically shows CK20-p53-CD44+ immunoprofile, while a CK20+p53+CD44- profile is characteristic of carcinoma in situ (the most important differential diagnosis), with CK20 being the most reliable marker. As with all immunohistochemical stain interpretation, very close correlation with morphology is essential due to varying immunoreactivity in a given case.

MULLERIAN LESIONS

a) **ENDOMETRIOSIS**

The bladder is the most common organ involved by endometriosis in the urinary tract. One percent of women with endometriosis have urinary bladder involvement and it typically occurs in women of reproductive age. Up to 50% have a history of pelvic surgery. Rarely vesical endometriosis has been reported in men with prostate carcinoma treated with estrogen therapy. Female patients most commonly complain of frequency, dysuria, and hematuria, and in 75% of cases these symptoms have catamenial exacerbations. A suprapelvic mass is palpable in 50% of the patients. Secondary and significant complications include obstruction of the ureteric orifices with secondary hydronephrosis or vesicocolic fistula. On **cystoscopic examination**, as many of 90% women have bladder abnormalities most commonly involving the posterior wall or trigone. The urologist typically describes an elevated, congested and edematous area in the mucosa overlying a translucent, blue-black or red brown area of discoloration. On rare occasion, the appearance may mimic cystitis glandularis or an unusual gross morphology of bladder cancer. On **gross examination**, it may form a mass involving the urinary bladder wall most often
secondary to muscle hypertrophy or fibrosis associated with endometriosis. If there is no mass, a hemorrhagic punctate may be observed if the glands are cystically dilated secondary to catamenial changes. On microscopic examination, it is composed of endometriotic glands and stroma. The endometrial glands are typically lined by cuboidal cells with eosinophilic cytoplasm and pseudostratified nuclei that may show mitotic activity depending of the phase of the cycle. The stroma may contain foamy histiocytes with some chronic inflammatory cells. The endometriotic stroma may be focally absent around some of the glands and in postmenopausal women that are not on estrogen replacement the diagnosis of endometriosis may be justify in the absence of endometrial stroma, as the latter becomes atrophic. In such instances, the glands still retain their endometriotic appearance. In some cases the endometrial stroma may be replaced by elastotic stroma similar to that seen in radial scars of the breast. The surface urothelium is not replaced by endometrioid-type epithelium as it may happen with endocervicosis. In the urinary bladder, malignant tumors have arisen in association with endometriosis, most commonly endometrioid and clear cell carcinomas. In such cases, the glands have typically a more complex architecture showing crowding, back to back, and cribriforming, there is more prominent cytologic atypia and a marked desmoplastic response in contrast to the endometrial stroma seen in endometriosis.

b) ENDOCERVICOSIS

It is well-known that non-neoplastic and neoplastic proliferations with müllerian differentiation may arise from the pelvic peritoneum (secondary müllerian system). Most of them show endometrioid differentiation (endometriosis and endometrioid tumors) or serous differentiation (endosalpingiosis and extraovarian serous tumors); lesions with endocervical-type differentiation are less common. Endocervicosis is composed of benign endocervical mucinous-type epithelium involving pelvic peritoneum, pelvic lymph nodes, urinary bladder, outer wall of uterine cervix and paracervical connective tissue, and vagina. Patients are typically reproductive age females that complain of suprapubic pain, dysuria, frequency, and hematuria with catamenial exacerbation of the symptoms. Some patients have a history of cesarian section. On cystoscopy, a mural mass (up to 5 cm) is frequently seen in the posterior wall or bladder dome covered by intact mucosa.

On gross examination, the lesion may have a non-descript appearance or may be seen as a rubbery mass with a spongy cut-surface with the cystic spaces containing clear mucus. On microscopic examination, there is a haphazard proliferation of glands throughout the bladder wall, typically centered in the muscularis propria, which may extent to the lamina propria or bladder serosa. However, the glands do not show crowding or back to back. The glands have irregular sizes and shapes, and are lined by a single layer of columnar cells with abundant pale mucinous cytoplasm (mucicarmine and PAS&D positive) and have a basally located small nucleus as seen in normal endocervical glands. Cells with a goblet-like appearance may be seen with the nucleus eccentrically compressed to the side. Some glands may contain ciliated cells or non-specific cuboidal cells intercalated with the mucinous cells, and in some cases, occasional endometriotic glands may be seen. Cytologic atypia is absent or at most mild and mitotic activity is exceptionally rare. The glands lumens contain mucus frequently admixed with acute inflammatory cells. In most instances, the endocervical-type glands are surrounded by normal or mildly hyperplastic smooth muscle, but they may be surrounded by fibrous or cellular stroma.
resembling endometrial stroma or elastotic stroma (atrophic endometriosis). In most cases, there is also an associated inflammatory infiltrate including foamy histiocytes. The glands may rupture resulting in mucin extravasation and more prominent stromal response. Immunohistochemical stains show apical positivity of the mucinous cells for CA 125 (antigen present in normal müllerian epithelia, including endocervical, endometrial and tubal epithelium); CEA, EMA, cytokeratin, and B72.4 are also positive.

The differential diagnosis includes:

**Cystitis glandularis intestinal type.** The glands tend to be more rounded, although may be cystically dilated and rupture resulting in mucin extravasation as described in endocervicosis. However, the glands are typically located in the lamina propria and do not involve the muscularis propria, they may be associated with a usual component of cystitis glandularis and are not associated with endometrial/elastotic type stroma, indicative of müllerian derivation.

**Urachal remnants.** Although located in the bladder dome, it is typically found in the apex or anterior aspect of the bladder dome and not in the posterior aspect as seen in endocervicosis. Furthermore, in contrast to endocervicosis, it forms a tortuous line indicating the presence of a single canal lined by mucinous epithelium that is surrounded by fibrous tissue which in turn is associated with layers of smooth muscle and finally an outer layer of connective tissue. The lining may also contain goblet cells but it does not have ciliated cells, endometrioid glands or endometrioid-type stroma.

**Primary adenocarcinoma.** Some bladder adenocarcinomas may have a deceptively benign histologic appearance; however the glands are present throughout the wall, with prominent involvement of the surface and lamina propria and not infrequently they have an associated transitional cell component of the tumor on the surface. The glands have angulated ends and elicit a desmoplastic response, the cells have at least focally more prominent cytologic atypia and they almost never contain abundant mucin unless the adenocarcinoma is of the signet-ring cell type, and in those cases there is abundant mucin extravasation.

**Metastatic adenocarcinoma.** Some endocervical adenocarcinomas may secondarily involve the bladder wall and be deceptively benign (adenoma malignum) and in a small biopsy may be difficult to be certain of the nature of the lesion. In cases of secondary involvement by a well-differentiated endocervical adenocarcinoma the patient should have other clinical symptoms and signs suggestive of the cervical origin of the tumor.

A primary adenocarcinoma may develop in a background of endocervicosis. In those cases, one can see transition from benign glands to dysplastic to frankly malignant glands.

c) MULLERIANOSIS

This entity is defined as a benign epithelial proliferation composed of an admixture of tubal, endocervical and endometrioid-type müllerian glandular epithelium outside the primary müllerian system. In the urinary bladder, this lesion typically involves the muscularis propria and lamina propria of the posterior wall and may form a tumor-like mass (up to 3 cm). Müllерianosis
is characterized by tubules and cysts with irregular sizes and shapes lined by ciliated cells intercalated with peg cells, next to endometriotic glands with endometrial stroma and/or a component of glands lined by columnar mucinous cells.

The differential diagnosis may include cystitis glandularis, cystitis cystica, and nephrogenic adenoma. As mentioned earlier, cystitis glandularis does not involve the muscularis propria, not cilia but urothelium is present lining some glands and endometriotic stroma is not seen. Nephrogenic adenoma typically shows a tubulocystic pattern, cilia or mucinous cells are not present, and in the bladder proper, NA does not involve the muscularis propria.

One patient reported by Donné and colleagues had symptomatic improvement after GnRH therapy. The authors postulated that the endometriotic component of the lesion became atrophic with tryptolerine, although the size of the lesion remained the same after six months of treatment.

POSTOPERATIVE SPINDLE CELL NODULE

This is a benign lesion initially described by Proppe, Scully and Rosai in the lower genitourinary tract in 1984. They studied 8 nodular lesions with a fascicular and proliferative appearance that developed between 5 weeks and 3 months after surgery and histologically superficially resembled a spindle cell sarcoma. Two of these cases occurred in the bladder wall. All postoperative spindle cell nodules are typically associated with a previous history of surgery. They may be an incidental finding during routine follow-up or patients may present with hematuria, urinary obstruction or other bladder symptoms. On cystoscopy, they are typically polypoid or nodular with poorly defined margins.

On gross examination, they may be soft or firm with a gray, yellow to tan cut-surface. On microscopic examination, they typically show a homogeneous appearance, being composed of intersecting fascicles with plump spindle cells and a delicate network of small vessels. These lesions often destroy and infiltrate the bladder wall mimicking a malignant tumor. They are typically densely cellular. The spindle cells are admixed with variable amounts of chronic inflammatory cells in the deeper areas of the lesion, while the superficial component is associated with an acute inflammatory infiltrate secondary to surface ulceration. Areas of edema, myxoid change or multiple small foci of hemorrhage are typically seen. At higher magnification, the cells have abundant eosinophilic cytoplasm. The nuclei are oval or spindle throughout the lesion, containing one or two small nucleoli and delicate chromatin, and mitotic activity may be brisk, up to 25/10 HPFs. However, no atypical mitoses or cytologic atypia are seen.

The differential diagnosis includes:

Leiomyosarcoma. The distinction may be difficult especially if the leiomyosarcoma is well differentiated as the histologic features may overlap. The clinical history of recent surgery at this site strongly suggests the diagnosis of spindle cell nodule over leiomyosarcoma. In these cases, close follow-up with subsequent biopsies is warranted.

Kaposi’s sarcoma: may enter in the differential diagnosis when the hemorrhage forms rows of clusters of red cells within slit-like spaces with the associated finding of hemosiderin-laden
macrophages and chronic inflammatory cells in a background of a spindle cell proliferation. However, there is an inconstancy and irregular distribution of these slit-like spaces in the postoperative spindle cell nodule.

**Benign reactive sarcoma-like processes** are rare in the bladder and the previous history of surgery is typically associated with the postoperative spindle cell nodule.

The cells of the postoperative spindle cell nodule are myofibroblasts by ultrastructure. The lesions have a benign clinical course and conservative treatment is recommended.

**INFLAMMATORY PSEUDOTUMOR**

This is a lesion intimately related to the postoperative spindle cell nodule, an important difference being that inflammatory pseudotumor does not have a previous history of surgery at the site where it develops. First recognized in the lung, it has received different names including pseudosarcomatous fibromyxoid tumor. There is some uncertainty regarding the pathogenesis of this lesion, ranging from reactive to neoplastic, the latter based on cytogenetic studies that have shown evidence for clonal origin. Patients range in age between 30 and 50 years, although it may occur at any age and it appears to be slightly more frequent in women. Gross hematuria is the most common presenting symptom, followed by bladder obstruction. However, some patients may be asymptomatic.

On **gross examination**, the lesions range from pedunculated masses protruding into the bladder cavity to nodules or ulcerating masses that deeply infiltrate the bladder wall. They are solitary with a broad base and may be as large as 37.5 cm. On **microscopic examination**, these lesions may show two different patterns: a) Disorganized, loose fascicles of spindle cells with a noticeable edematous-myxoid background and a prominent vascular network composed of small capillaries (resembling nodular fasciitis), b) Cellular areas with intersecting fascicles of spindle cells and variable amounts of intercellular collagen. Some authors find this pattern more commonly deep in the lesion. On high power examination, the cells are elongated with tapering eosinophilic cytoplasmic processes. Stellate cells and more polygonal cells may also be seen, especially in the more myxoid areas. There is no striking pleomorphism. The nuclei are oval to spindled-shaped with open chromatin and one or multiple apparent nucleoli. There is no marked cytologic atypia and mitotic activity although present (up to 4/10 HPFs) is not as prominent as seen in postoperative spindle cell nodule. There is an inflammatory infiltrate, more commonly composed of eosinophils, lymphocytes and plasma cells. The latter can be quite prominent imparting an appearance reminiscent of a plasma cell granuloma variant of inflammatory pseudotumor. Two worrisome features associated with these lesions are: 1) Frequent wall invasion (may reach the outer aspect of the muscularis propria), and 2) Presence of small areas of necrosis, findings that always raise the possibility of a malignant process. The finding of necrosis at the tumor-detrusor muscle interface is not found in inflammatory pseudotumor but it is indicative of a malignant process.

The **immunohistochemical profile** of the inflammatory pseudotumor is similar to that of the postoperative spindle cell nodule. Both lesions are vimentin positive, frequently positive for keratin, smooth muscle actin, and may be positive for EMA and desmin. They are typically
negative for CK 34betaE12 and CK 5/6, and p63. Recently, it has been shown that the inflammatory pseudotumor is frequently positive for ALK-1. The chromosome 2p23 is the site of the human ALK gene, which codes for anaplastic lymphoma kinase. ALK is a tyrosine kinase receptor and a member of the insulin growth factor receptor superfamily and clonal abnormalities of ALK are typically associated with anaplastic large cell lymphoma. The significance of this finding in inflammatory pseudotumor it is not clear at present time, although it has been shown to be more frequently express in patients under the age of 40 years. Some inflammatory pseudotumors show weak p53 expression. These lesions are typically diploid and by electromicroscopy the lesion has a myofibroblastic lineage.

The differential diagnosis includes:

**Myxoid leiomyosarcoma:** This malignant tumor is typically seen in an older group of patients (mean 50 years). These tumors present as large exophytic tumors or infiltrating masses and are composed of long intersecting fascicles with elongated cells that have eosinophilic cytoplasm and cigar-shaped nuclei. The tumors are hypocellular throughout and the presence of myxoid background is a typical finding, these features overlapping with those seen in inflammatory pseudotumor. By definition, these neoplasms have an infiltrative border, typically show areas of necrosis (of help if present at the tumor-detrusor muscle interface) and are associated at least with moderate cytologic atypia and brisk mitotic activity in most cases especially in the more cellular areas. Associated inflammation and vascularity are not typical features of myxoid leiomyosarcoma but seen in inflammatory pseudotumor. If inflammatory cells are present are typically neutrophils. From the immunohistochemical point of view, these tumors are positive for vimentin, actins, but less frequently for desmin. They are also frequently positive for keratins CK but also negative for 34betaE12 and CK 5/6. Finally, although leiomyosarcomas may be positive for EMA, the frequently is lower than that seen in inflammatory pseudotumor and they are typically ALK negative.

**Sarcomatoid carcinoma:** It occurs in an old population (mean age: 70 years). These tumors have a heterogeneous gross appearance and on microscopic examination they typically have a component of conventional transitional cell carcinoma, carcinoma in situ, squamous cell carcinoma, or small cell carcinoma that merges with the sarcomatoid component. Jones and colleagues reported a series of sarcomatoid carcinomas that were associated with a prominent myxoid background as seen in inflammatory pseudotumor. These tumors characteristically have a gelatinous cut-surface and on microscopic examination display polygonal epithelial cells that alternate with spindled epithelial cells with a fascicular growth pattern. Confluent necrosis as well as deep invasion of the bladder wall is present in most cases. The most characteristic finding is the presence of this myxoid background (Alcian blue positive), which may have a focal or diffuse distribution, associated with a delicate vasculature resembling to some extent granulation tissue. These tumors may also show extensive areas of sclerosis. Cytologically, there is marked atypia, although may be focal, with large cells showing hyperchromatic nuclei and coarse chromatin. The cytologic atypia is accompanied by brisk mitotic activity and presence of atypical mitotic figures. If a small sample of tissue is available and only contains these myxoid areas the differential diagnosis with an inflammatory pseudotumor may be very difficult as these areas typically show bland nuclear features. In fact, one of the cases reported by Jones and colleagues was interpreted by the outside pathologist as
an inflammatory pseudotumor/postoperative spindle cell nodule in the cystectomy specimen of a man, who a few weeks before had been diagnosed with a moderately differentiated transitional cell carcinoma in a TUR specimen. Six months later, the patient presented with a pelvic that revealed a malignant spindle cell tumor. After reviewing the case, the final diagnosis was myxoid and sarcomatoid carcinoma. Helpful features in establishing the diagnosis of carcinoma in these cases include the finding of a conventional carcinomatous component, confluent necrosis and focal marked cytologic atypia. These tumors are usually positive for keratins and EMA, although the sarcomatoid component may be negative or only focally positive. As a consequence the diagnosis is based on morphology and clinical features of the tumor. These neoplasms are positive for vimentin and may express, although infrequently, muscle actins and desmin. Sarcomatoid urothelial carcinoma is positive for keratins including CK 34betaE12 and CK5/6, p63 in about half of the cases but it is ALK negative. Thus in the differential diagnosis of inflammatory pseudotumor, leiomyosarcoma and sarcomatoid carcinoma, a combination of pankeratin, SMA, and ALK positivity favors inflammatory pseudotumor; expression of several cytokeratin and especially CK 34betaE12 and CK 5/6 with p63 favors sarcomatoid carcinoma and SMA positivity with overall absence of other markers favors leiomyosarcoma.

**Inflammatory fibrosarcoma:** This tumor may involve the bladder by extension from an intraabdominal site. In contrast to the inflammatory pseudotumor, the spindle cells have malignant nuclear features and a denser and uniform fascicular growth pattern resembling that of a leiomyosarcoma.

**Malignant fibrous histiocytoma:** These tumors occur rarely in the urinary bladder, they typically show a storiform growth, have an admixture spindle and multinucleated cells associated with lymphocytes. These tumors are typically keratin and EMA negative.

**Postoperative spindle cell nodule:** These are more cellular and have a previous history of surgery as discussed earlier.

Inflammatory pseudotumor may recur but typically does not metastasize. It is important to remember that the diagnosis of inflammatory pseudotumor of the bladder should be made with caution in cases where there is no previous history of surgery especially in older patients.
References:

Young RH. Pseudoneoplastic lesions of the urinary bladder and urethra: A selective review with emphasis on recent information. Sem Diagn Pathol 1997;14:133-46.

Cystitis Glandularis:

Nephrogenic adenoma:
Sesterhenn IA, Davis CJ, Mostofi FK. Nephrogenic adenomas of bladder and urethra. Lab Invest 1984;50:53A.


Young RH. Nephrogenic adenomas of the urethra involving the prostate gland: a report of two cases of a lesion that may be confused with prostatic adenocarcinoma. Mod Pathol 1992;5(6):617-20.


**Radiation induced cystitis**


**Endometriosis:**


**Endocervicosis:**

Young RH, Clement PB. Endocervicosis involving the uterine cervix: a report of four cases of a benign process that may be confused with deeply invasive endocervical adenocarcinoma. Int J Gynecol Pathol 2000;19:322-3.

**Mullerianosis:**


**Postoperative spindle cell nodule inflammatory pseudotumor:**


