12 Bladder

Bladder biopsy specimens are usually submitted to rule out a urothelial neoplasm. The procedure may be indicated because of hematuria, an abnormal urine cytology, a history of urothelial neoplasm, or a lesion seen on cystoscopy. The cystoscopic impression is important, and you usually do not diagnose a papillary lesion if none was seen by the urologist. The bladder biopsy specimen is typically a tiny tissue fragment, so you should look at each level carefully.

The normal urothelium consists of a stratified nonsquamous epithelium, also called *transitional cell epithelium*. It consists of a five- to seven-cell thick layer of uniform cells that do not significantly mature as they reach the surface (unlike squamous epithelium) and that tend to have oblong nuclei oriented perpendicular to the surface (Figure 12.1). The nuclei are about two to three times the size of lymphocytes. Mitoses are usually seen only at the basal layer, but in the presence of inflammation and reactive changes they may be seen throughout. At the surface is a specialized cell layer called the *umbrella cells*, large pillowy cells that appear wider than the underlying urothelial cells. Umbrella cells may have atypical nuclei and should be ignored when assessing the urothelium for neoplasia.

Underneath the urothelium lies the lamina propria, a connective tissue layer that has vessels, lymphatics, occasional smooth muscle fibers, and even occasional fat. Deep to this is the thick muscularis propria, also known as the *detrusor muscle*. Beyond the muscular wall is either adventitia or, where the bladder lies against the peritoneum, peritonealized serosa.

Normal Variants

Some changes in the bladder are so common that they are essentially normal. One of these changes is the formation of *von Brunn's nests*, which are downward invaginations of the urothelium into the lamina propria (Figure 12.2). These can look alarmingly like urothelial nests that are invading the bladder, but they should have bland urothelium that looks just like normal urothelium (see below for a description of neoplastic urothelium) and have a smooth rounded border. As these nests progress, they may acquire a dilated central lumen (*cystitis cystica*), columnar cell metaplasia (*cystitis glandularis;* see Figure 12.2), and even intestinal metaplasia with mucin production. They are still benign. However, just as high-grade squamous intraepithelial lesions can involve endocervical glands, in situ urothelial carcinoma can grow down into von Brunn's nests, mimicking invasion. Another normal variant is the formation of squamous metaplasia, especially in the trigone area of the female bladder.

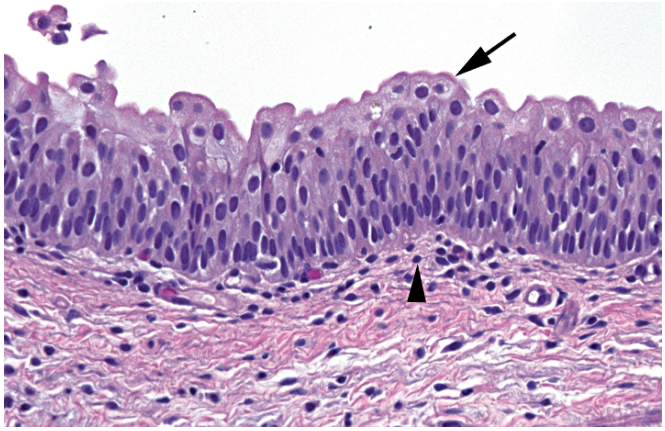

Figure 12.1. Normal urothelium. The urothelial cells form a layer five to seven cells thick, with large umbrella cells sitting on top (arrow). The urothelial nuclei are generally polarized and oriented perpendicular to the surface, with the exception of the umbrella cells. The nuclei are two to three times the size of a lymphocyte (arrowhead).

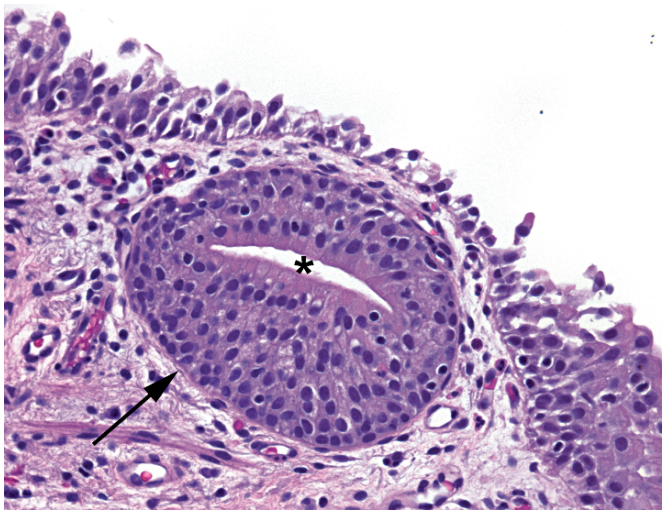

Figure 12.2. Von Brunn's nest and cystitis glandularis. The normal urothelium has invaginated down into the lamina propria, forming a rounded von Brunn's nest (arrow). The center of the nest has acquired a lumen and columnar cell metaplasia (asterisk), which is known as *cystitis glandularis*.

Inflammation (Cystitis)

There are several types of inflammatory disease that you may see. One is *granulomatous cystitis*, which once was largely caused by tuberculosis but is now more likely to be secondary to Bacillus Calmette-Guerin (BCG) therapy—a topical chemotherapy for urothelial carcinoma. The intravesical injection of BCG causes an intense inflammatory response that may wipe out the carcinoma.

Parasitic infection, most commonly by *Schistosoma* species, is still common in undeveloped countries but rare in the United States. The inflammatory response is actually not caused by the organisms but by their eggs, which are extruded into the bladder wall and cause intense foreign-body reaction. *Polypoid cystitis* is similar to an inflammatory polyp of the bladder and is associated

with any process that injures the bladder (e.g., indwelling catheters, calculi, fistula from the colon). *Interstitial cystitis* is a poorly understood disease that is mainly a cystoscopic diagnosis and more a diagnosis of exclusion for the pathologist.

Malakoplakia is one of those mysterious rare entities that most residents do not see, think about, or understand until they are studying for boards. It is a descriptive name for the yellow plaques seen on cystoscopy, which are formed by sheets of epithelioid histiocytes sporting characteristic round inclusions called Michaelis-Guttman bodies (they look like archery targets). It is caused by a defective macrophage response to infection.

Urothelial Neoplasms

Urothelial neoplasms are categorized into two cancer pathways: *flat* and *papillary*. Both can lead to invasive carcinoma, but the terminology is different. About 90% of bladder carcinomas are urothelial, so this will be the focus of this chapter.

Flat neoplasia does not form an exophytic lesion but may still be visible on cystoscopy as a red area. It progresses through dysplasia (rarely diagnosed) to carcinoma in situ. Flat urothelial carcinoma in situ is just known as *carcinoma in situ* (CIS) and can go on to high-stage invasive carcinoma without ever making an exophytic lesion, so always scrutinize the urothelium at high power, especially in denuded areas. Features of CIS include the following:

- Urothelial cells have increased nuclear size. A helpful hint is that the worst nuclei of CIS should be four to five times the size of lymphocyte nuclei (Figure 12.3).
- There are Hyperchromatic nuclei with irregular ("boulder-like") outlines.
- The urothelium has a tendency to fall apart, appearing denuded, with a few clinging cells.
- Full-thickness involvement is *not* a requirement to diagnosis CIS (even scattered malignant cells with the above features justify a diagnosis of CIS).

If a lesion has atypia that you think is neoplastic (i.e., not reactive) yet the cells are not bad enough to call CIS, then the diagnosis of dysplasia is appropriate. However, the options are limited: you should not call mild dysplasia, as urologists do not treat it, nor should you call severe dysplasia, which is the same as CIS. True dysplasia (meaning moderate dysplasia) is an uncommon diagnosis, with most bladder biopsies signed out as normal, CIS, or reactive.

Papillary neoplasia has a much wider spectrum of disease, from benign papilloma to high-grade carcinoma. The papillary lesions are unusual in nomenclature, however, in that despite being *in situ lesions*, they are conventionally just called *noninvasive papillary urothelial carcinoma*, either low or high grade. If you use the word *in situ* to refer to papillary lesions,

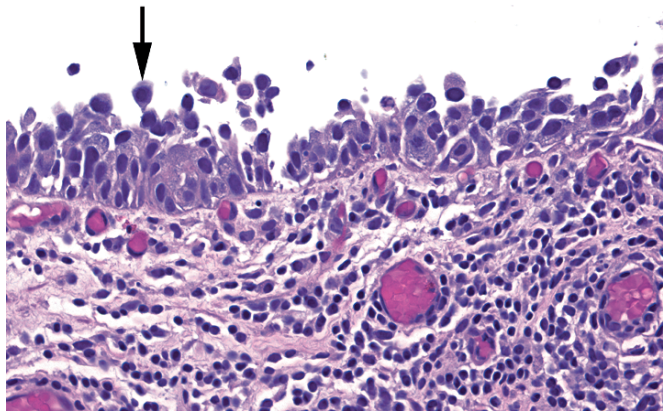

Figure 12.3. Flat carcinoma in situ. The urothelium is partially denuded (stripped of cells), but the cells that remain show enlarged, round, hyperchromatic nuclei appearing to pop off the surface (arrow). Compare the nuclear size to the underlying lymphocytes.

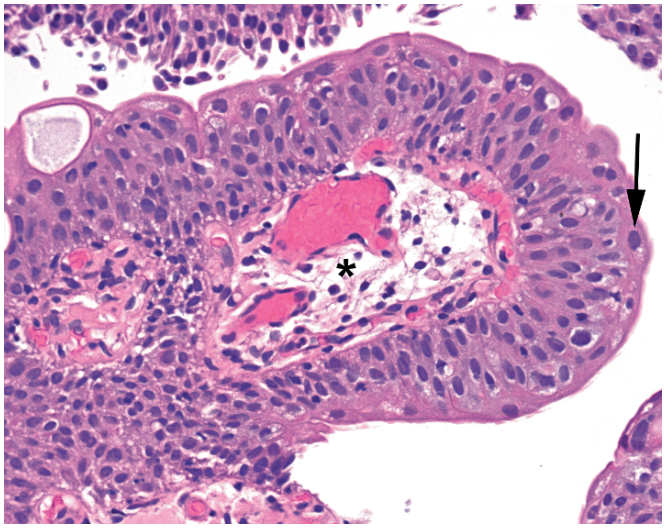

Figure 12.4. Papilloma. There is a prominent fibrovascular core (asterisk), and the urothelium resembles normal urothelium both in thickness and in bland cytology. Some large umbrella cells are visible (arrow).

urologists think you mean CIS. Once these cancers invade, they are called *invasive papillary urothelial carcinoma* and are typically high grade.

Papillary lesions all have in common a branching architecture with delicate fibrovascular cores, and they can get quite large, even filling the bladder. The classification is determined by the cytology of the urothelial lining.

Papilloma

Papillomas are defined by having a normal urothelial lining (normal thickness, well-organized and polarized, and small nuclei, often with nuclear grooves, without mitoses; Figure 12.4). They tend to be small lesions. There is no risk of malignant transformation.

Do not be fooled by papillary hyperplasia, which is an undulating wave-like urothelium without true fibrovascular cores.

Papillary Urothelial Neoplasm of Low Malignant Potential

"Papillary urothelial neoplasm of low malignant potential" (PUNLMP) was recently added to the World Health Organization classification with the intent of creating a category for those proliferative neoplasms that are larger and fuller than papillomas but do not look malignant. The urothelial lining is increased in thickness but still appears well organized, with all nuclei streaming in parallel, and has near-normal nuclear/cytoplasmic ratios (Figure 12.5). Mitoses should be exceedingly rare and confined to the basal layer, as in normal urothelium.

Low-Grade Papillary Urothelial Carcinoma

Low-grade papillary urothelial carcinomas (Figure 12.6) have the following features:

- The urothelial lining is increased in thickness and is still in general fairly organized (the cells are still mostly polarized with respect to the surface).
- There is scattered subtle nuclear atypia consisting of random slightly enlarged darker nuclei, in contrast to PUNLMP, in which every nucleus looks the same.
- Mitoses are uncommon, but typically you will see some of them, in contrast to PUNLMP.

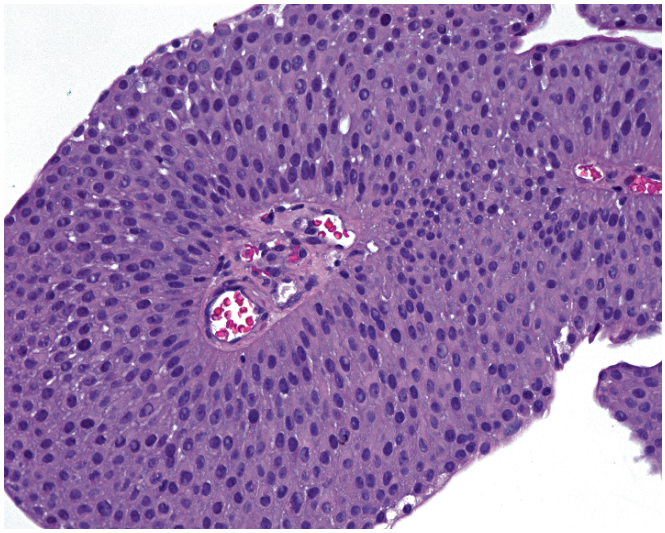

FIGURE 12.5. Papillary urothelial neoplasm of low malignant potential. This papillary lesion shows an increased thickness relative to normal urothelium, but the cells remain uniform and organized.

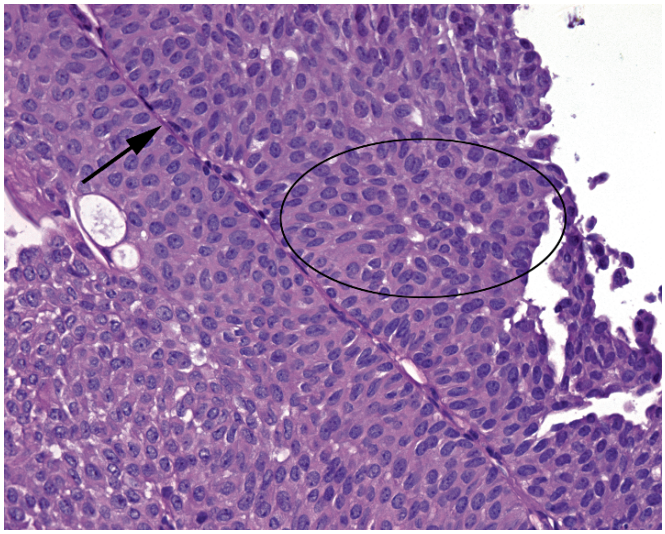

FIGURE 12.6. Low-grade papillary urothelial cancer. The fibrovascular cores (arrow) are lined by urothelium that is thicker than normal, increasingly disorganized (circle), and with enlarged nuclei.

High-Grade Papillary Urothelial Carcinoma

High-grade papillary urothelial carcinoma lesions are lined by cells that look like CIS. They can be noninvasive, but you have to look carefully for associated invasion, which is often present.

- The urothelium is very disorderly, with little nuclear orientation to the surface.
- Nuclei are enlarged, hyperchromatic, and pleomorphic and may have nucleoli (Figure 12.7).
- Mitoses are seen at all levels of the epithelium (in a well-oriented fragment).
- Focal nonurothelial differentiation (squamous or glandular) is possible.
- A small amount of high-grade characteristics (>5%) generally defines the entire lesion as high grade.

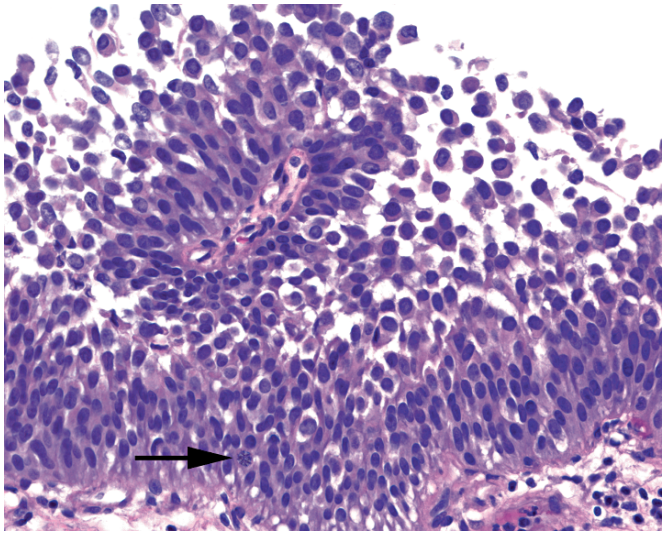

Figure 12.7. High-grade papillary urothelial cancer. This papillary lesion shows large, dark, pleomorphic nuclei popping off the surface, similar to carcinoma in situ (see Figure 12.3). A large mitotic figure is visible (arrow).

Invasive Urothelial Carcinoma (Formerly "Transitional Cell Carcinoma")

Most invasive carcinomas arise in the setting of either high-grade papillary urothelial carcinoma or CIS. Identifying invasion into the lamina propria relies on similar cues as found in other organs:

- Irregular tongues of cells or single cells pushing into the lamina propria
- "Paradoxical differentiation": the deep invasive cells acquire increased pink cytoplasm, mimicking maturing surface cells (Figure 12.8)
- Retraction artifact: the apparent cracking of the stroma away from tumor nests
- Desmoplastic response of stroma (however, often not present)

Identifying the muscularis propria (detrusor muscle), and whether the tumor invades that deeply, is critically important. Superficial carcinomas that do not invade the muscularis propria may be treated conservatively by transurethral resection (TURBT) or topical chemotherapy. Invasion of the detrusor buys the patient a cystectomy. Therefore, any diagnosis of invasive carcinoma should state whether the detrusor is (1) present on the biopsy and (2) involved. Remember that wisps of smooth muscle (the discontinuous muscularis mucosae) may be found in the lamina propria, so do not overcall detrusor invasion on that basis. The detrusor is a big slab of muscle, relatively speaking (Figure 12.9).

Also, as mentioned earlier, ugly urothelium that invades the lamina propria in broad round nests may actually be growth of CIS into von Brunn's nests or an inverted growth pattern of a noninvasive papillary urothelial carcinoma (see the following list). The difference is that in these mimickers of invasion the nests are round and even without ragged borders, and they appear basophilic, often with crowding or palisading of the outermost layer of cells.

- Conditions that look like cancer but are not
  - Inverted papilloma: As in the nose (Schneiderian papilloma), a papilloma can occasionally grow down and in, instead of up and out, creating an inside-out or inverted papilloma that is buried in stroma but does not cross the basement membrane. Like von Brunn's nests, the urothelium should look benign, but the nests may be very closely packed into a small area or coalesced into anastomosing cords.

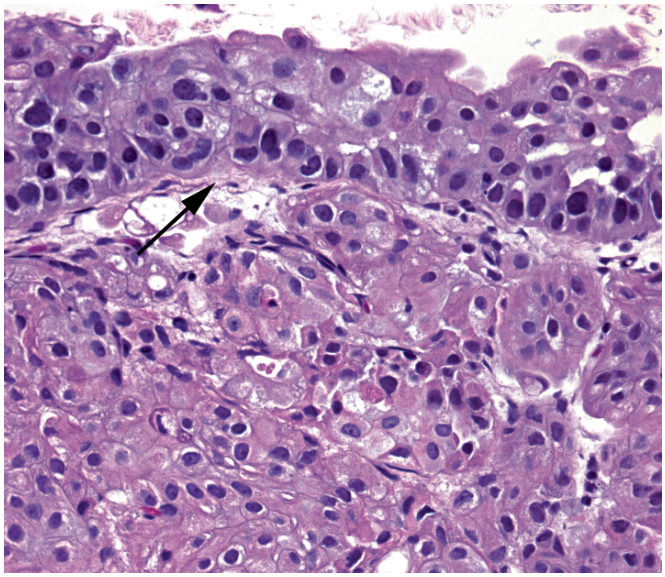

Figure 12.8. Invasive urothelial carcinoma. In this case, the carcinoma is arising out of flat carcinoma in situ, seen above the basement membrane (arrow). The nests of tumor in the lamina propria appear more pink than the surface carcinoma in situ, corresponding to paradoxical differentiation.

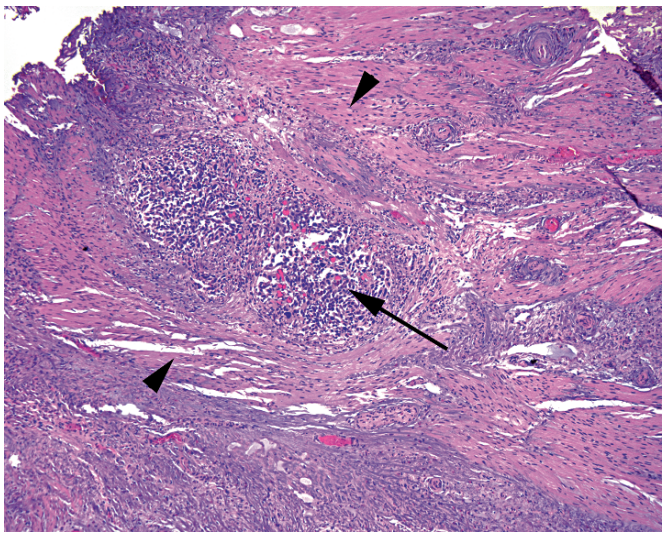

Figure 12.9. Carcinoma in detrusor muscle. Thick bands of muscle (arrowheads) are seen on either side of a nest of tumor cells (arrow).

- Reactive changes in urothelium: As in other organs, reactive changes tend to create enlarged but euchromatic nuclei; the chromatin should be evenly blue grey and the nuclear contour smooth and oval, yet nucleoli may be very large (Figure 12.10). You should raise your threshold for CIS in the presence of extensive inflammation.
- Nephrogenic adenoma: Nephrogenic adenoma is a benign proliferative neoplasm that can take on many appearances, including cuboidal cells lining papillae, hobnail cells lining vessel-like structures (Figure 12.11), small infiltrative-looking tubules, sometimes with

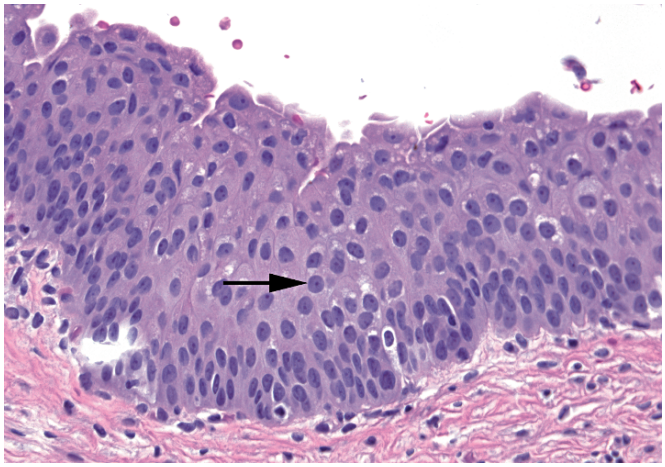

Figure 12.10. Reactive nuclei. These urothelial nuclei are somewhat enlarged and have prominent nucleoli (arrow) but retain a smooth nuclear outline and pale, even chromatin. They are benign.

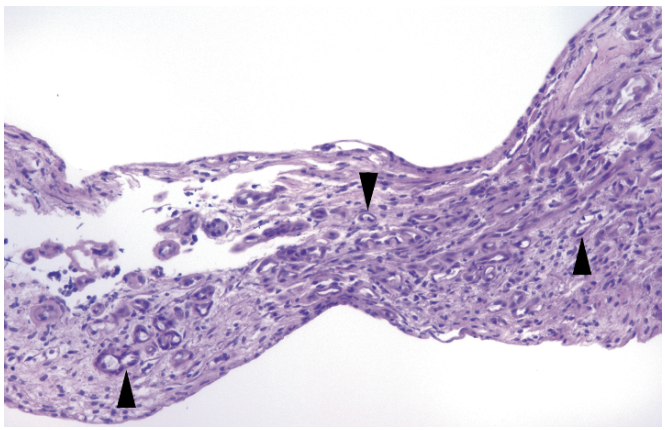

Figure 12.11. Nephrogenic adenoma. In this bladder biopsy specimen, there are multiple tiny tubules in the lamina propria (arrowheads) with prominent dark nuclei. The urothelium is not seen here.

thyroid-like accumulations of colloid, and small tubules mimicking signet-ring cell carcinoma. In all cases, these differ from urothelial lesions by being a single-layered cuboidal epithelium. There may be focal large dark nuclei, but they should have uniform dense chromatin and no mitoses.

- Conditions that look benign but are not
  - Nested transitional cell carcinoma: This is an invasive urothelial carcinoma made of small, bland nests in the lamina propria that, despite looking like von Brunn's nests, is actually an aggressive carcinoma. Great, right? Features suggestive of this lesion include an infiltrative pattern at the base of the lesion, as well as an architecturally complex pattern of closely packed small nests.
  - Lymphoepithelial-like carcinoma: While this certainly does not look like normal bladder, lymphoepithelial-like carcinoma can be very sneaky to the pathologist in training. The overall impression is that of raging inflammation and tissue destruction, with sheets

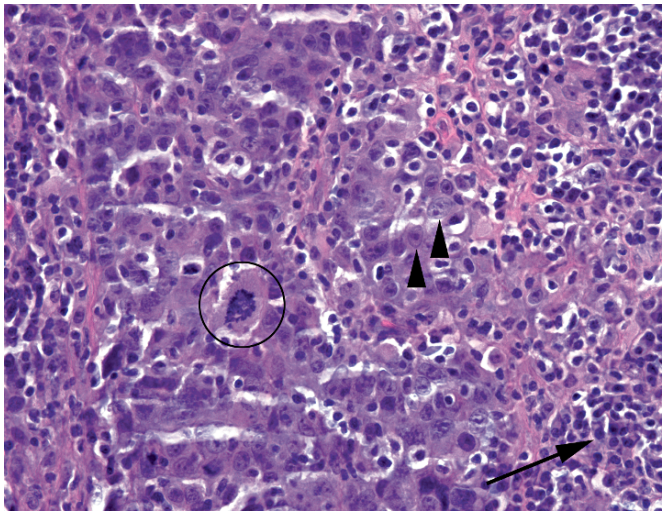

Figure 12.12. Lymphoepithelial-like carcinoma. The malignant cells (arrowheads) are almost obscured by the background of lymphocytes (arrow). Atypical mitoses are present (circle).

of lymphocytes, but the actual carcinomatous cells tend to fade into the background on H&E stain. The nuclei tend to be large and bubbly, but not particularly hyperchromatic or carcinoma-like, and the cytoplasmic borders are very indistinct, almost syncytial (Figure 12.12). A cytokeratin stain is helpful.